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POSTGRADUATE EDUCATIONAL ISSUE

A SYMPOSIUM ON BRAIN ISCHAEMIA

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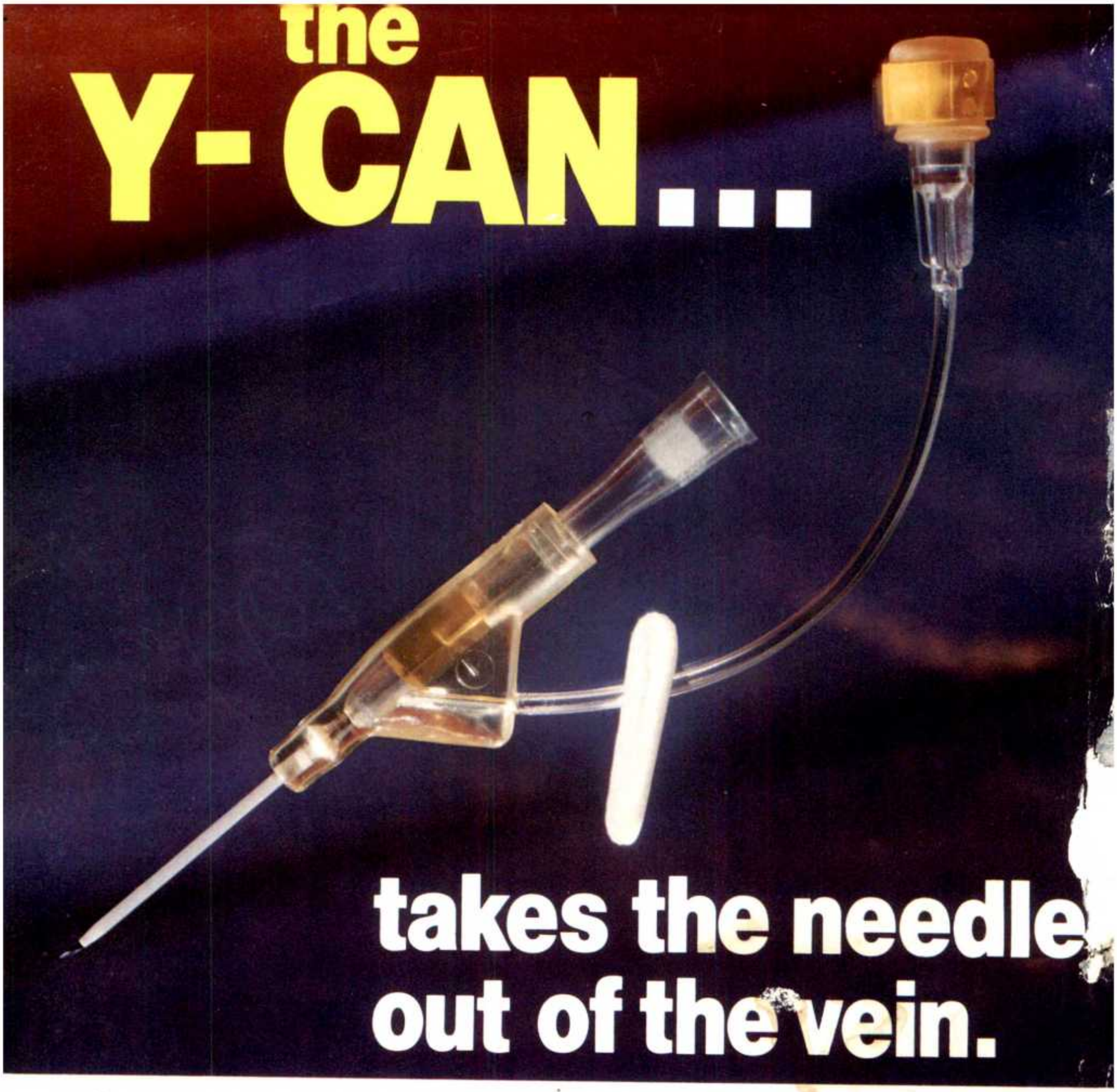
D G McDOWALL



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References

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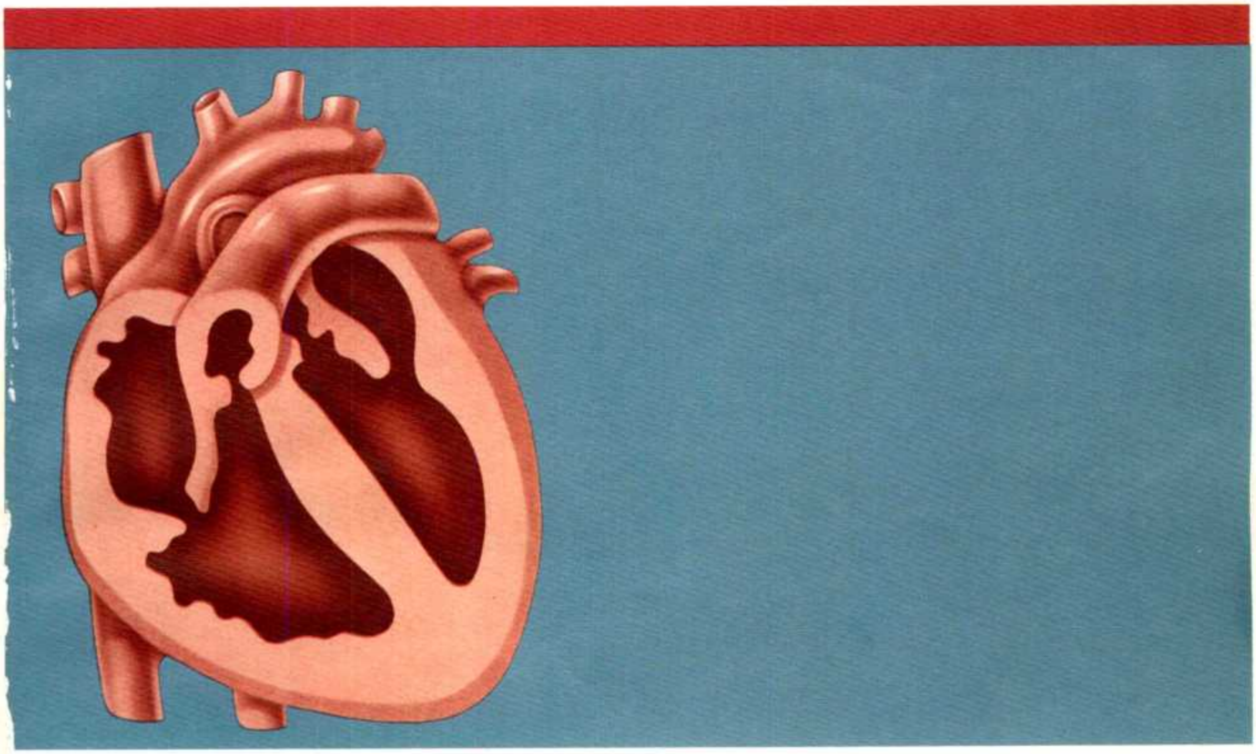

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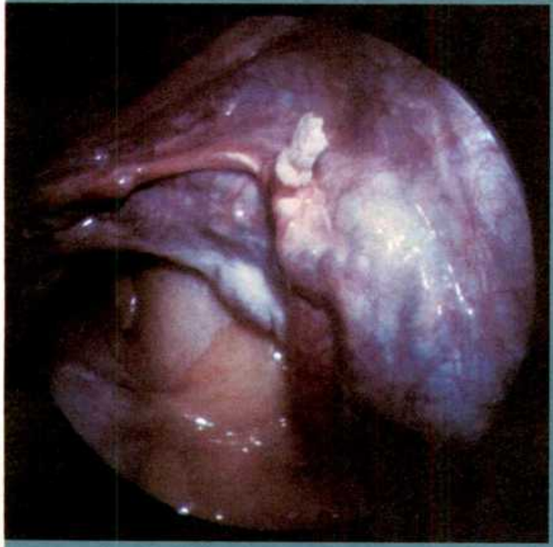

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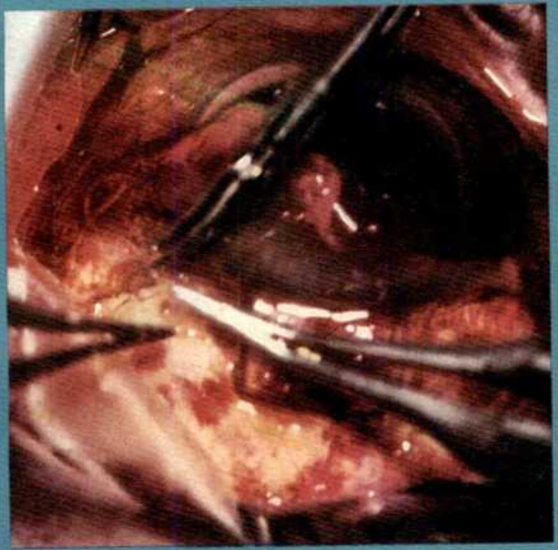

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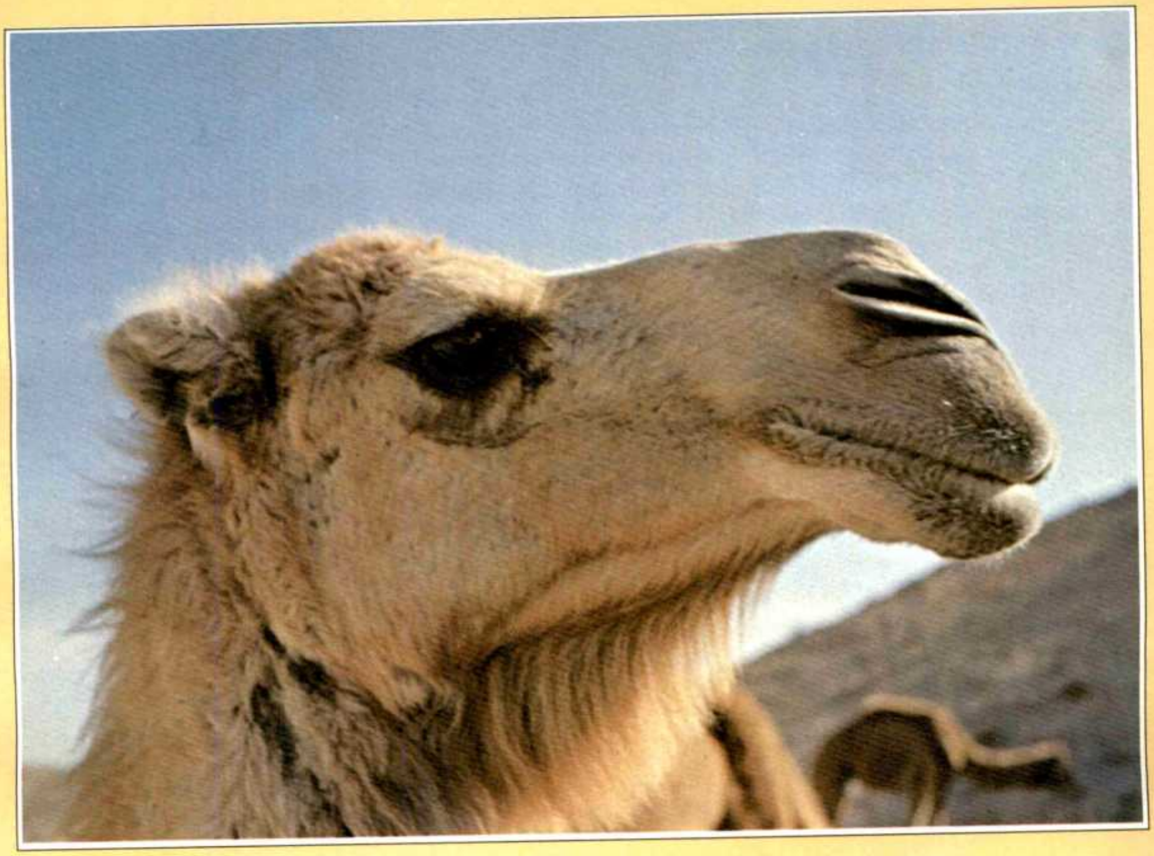

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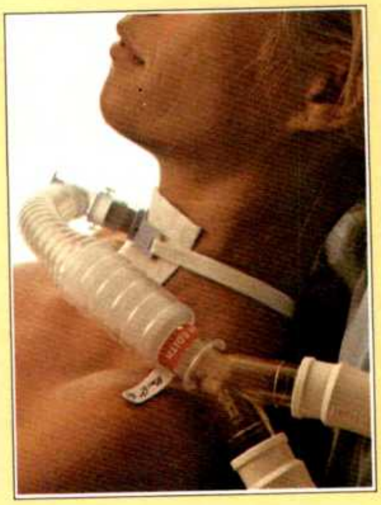

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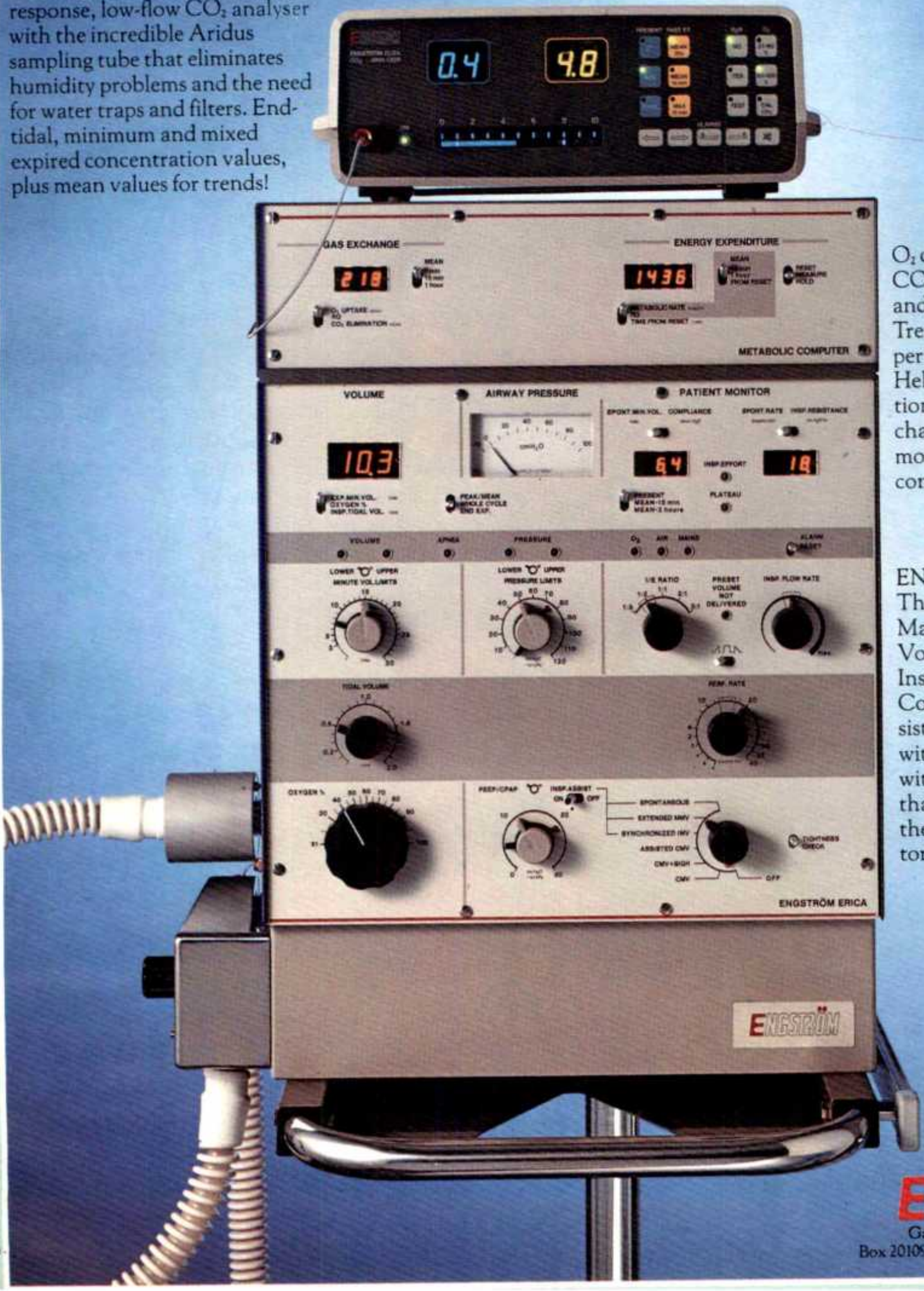

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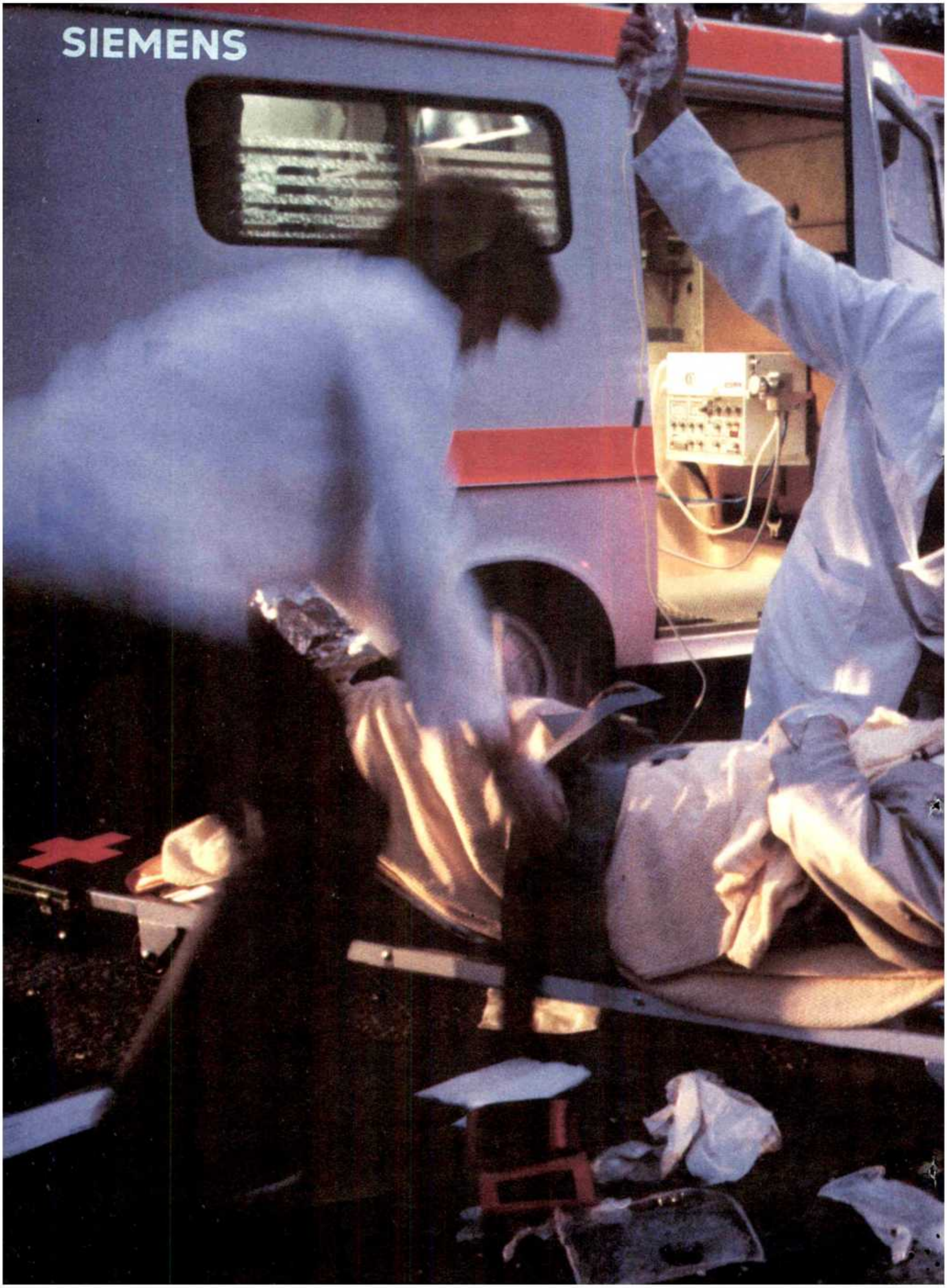
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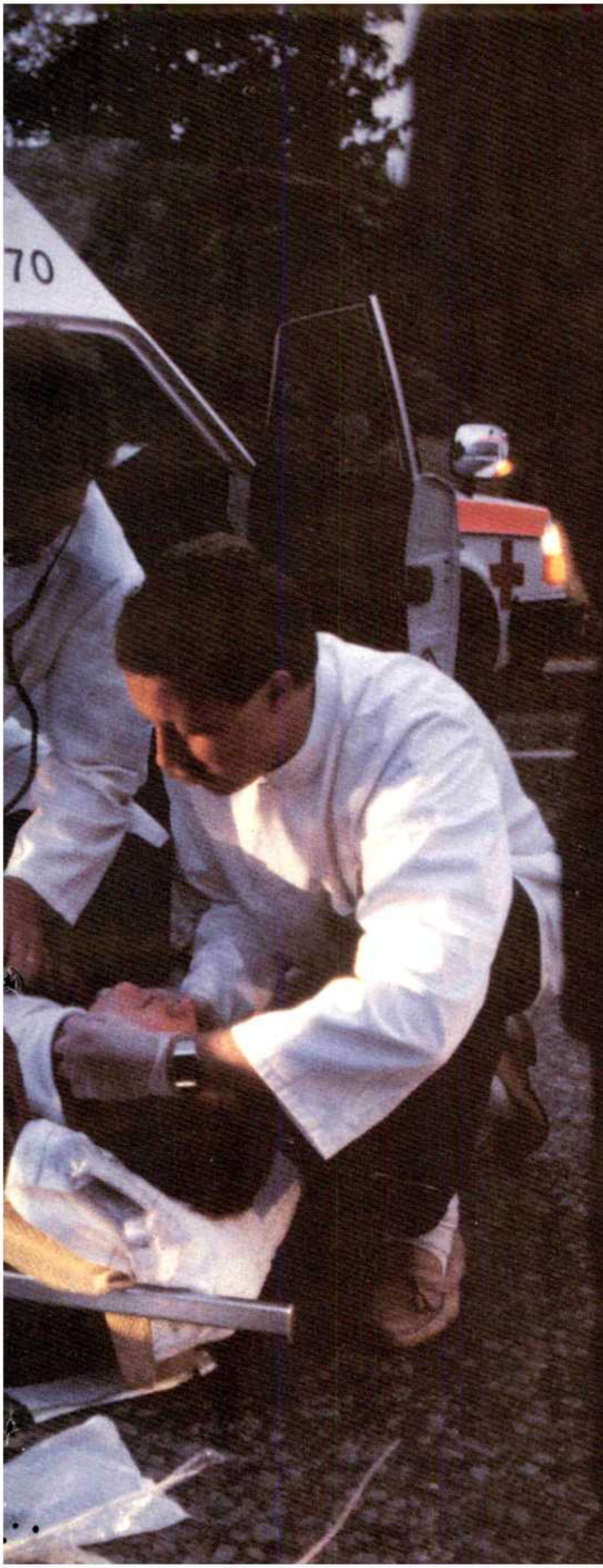

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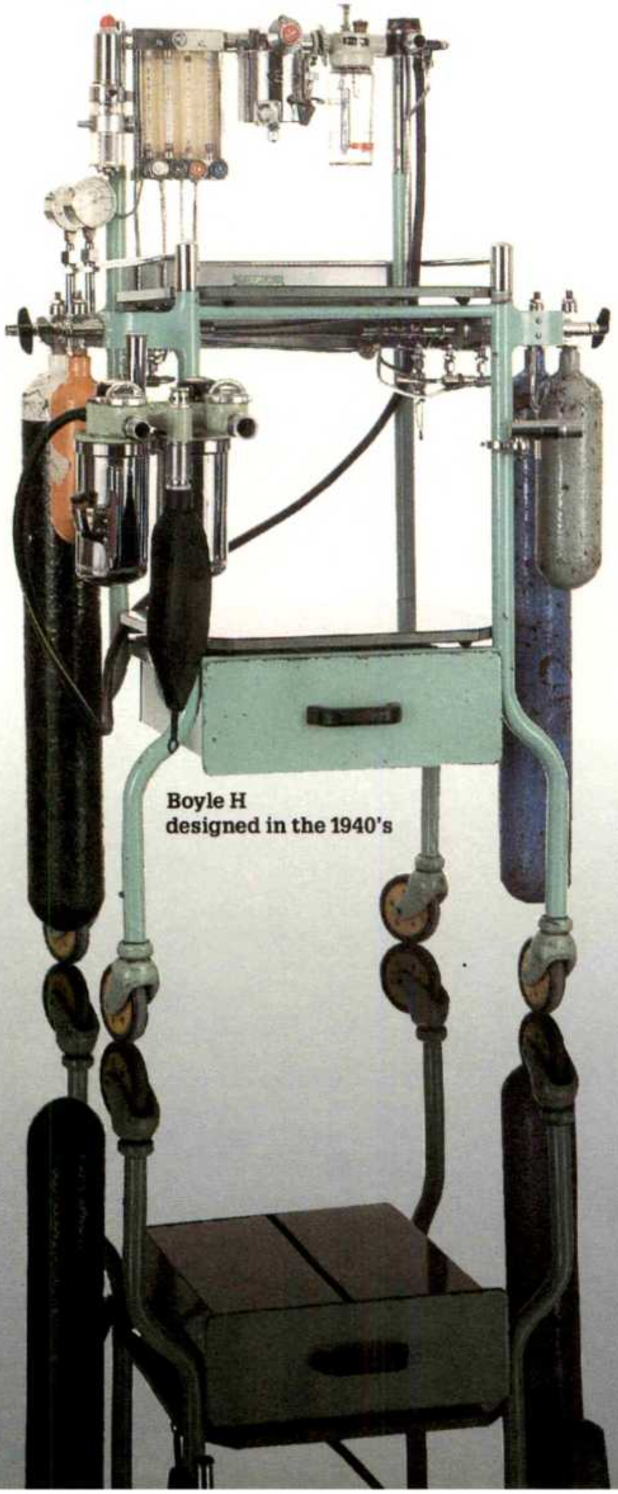

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BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

BRAIN ISCHAEMIA—ITS PREVENTION AND TREATMENT

Anaesthetists are involved regularly in the management of patients who have suffered brain ischaemia, for example following circulatory arrest, head injury or hypoxia secondary to pulmonary dysfunction. Furthermore, the anaesthetic use of induced hypotension, deliberate circulatory arrest in cardiac surgery and local cerebral circulatory arrest in neurosurgery require an understanding of the tolerable limits of such brain "insults". There has been considerable progress in elucidating the pathophysiology of brain ischaemia and some advances in therapy. Undoubtedly, however, the best treatment is still prevention and, to that extent, the anaesthetist needs to keep abreast of developments in the monitoring of brain function.

The *British Journal of Anaesthesia* promoted a Workshop attended by the authors of the papers in this issue, together with additional invited experts at which each review paper was discussed with particular emphasis on the anaesthetic relevance of the points raised. In this Editorial, major points made in that discussion and not covered within the papers are included.

Graham opens this issue with an account of the pathophysiology of brain ischaemia in which he describes the development of the histological changes over hours and days, a time-scale which encourages hopes of therapeutic intervention in the process. One component of the post-insult condition which the anaesthetist attempts to treat is brain swelling, part of which results from cerebral oedema. Klatzo classifies the types of brain oedema and explains the mechanisms of each, and the reader will gain an understanding of the temporal sequence of events in post-ischaemic brain swelling on which to build a logical strategy of treatment. Klatzo emphasizes that hypertension at times when the blood–brain barrier is open will worsen vasogenic oedema, while hypotension in the presence of high tissue fluid pressure will result in further ischaemia and he therefore advocates the careful maintenance of normotension. However, in some patients with developing focal ischaemia, for example a progressing monoparesis following aneurysm clipping, deliberate hypertension is known to produce clinical improvement. The situation is complex, but all are agreed that hypotension is bad and most accept that normotension is usually wise, but that in individual cases the clinical response to induced hypertension should be assessed in focal ischaemia. Symon emphasized in the Workshop that, before inducing hypertension he would exclude actual infarction indicated as brain shift on the CT scan, which is an absolute contraindication to increasing the arterial pressure. Graham stressed that, after total circulatory arrest, brain swelling is only moderate and does not induce shift or impaction. Furthermore, major increases in ICP are uncommon after circulatory arrest, although it must be admitted that the amount of ICP data in this circumstance is small. Brain swelling and oedema with increased ICP are commonly seen in focal or regional brain ischaemia, for example strokes and head injury.

Symon, and Heuser and Guggenheimer describe the flow thresholds in brain ischaemia for electrical failure (EEG and evoked potentials) for ionic shifts resulting from membrane dysfunction and for water accumulation within the brain. Of particular interest to anaesthetists is the possibility of lowering these thresholds with drugs, for example reducing the blood flow at which electrical or ionic failure, or both, occurs and the effects of barbiturates, prostaglandin inhibitors and calcium entry blockers amongst others, are considered in these papers. In the discussion at the Workshop it was clear that there is a re-awakening of interest in the role of "mild" hypothermia with central temperatures of 33–36 °C on the ischaemic process, since there are suggestions in the literature of a protective effect of such small and easily-achieved reductions in body temperature.

Clinically, what matters is neuronal cell death, and the ionic changes are but steps on the road to that event. The nearest ionic change in terms of flow threshold is the movement of calcium ions into the cell and the resultant increase in free calcium may have a causal connection with histological change. The method of Meldrum and colleagues for visualizing abnormal intracellular accumulation of calcium does not relate to the calcium entry at ischaemic thresholds, but probably reflects later calcium entry into the cells in the recovery phase, particularly if seizure activity occurs in the neurones. Meldrum and colleagues conclude that post-ischaemic seizure activity must be suppressed and this is supported by clinical experience. It is particularly important to monitor post-seizure activity in patients being managed by controlled ventilation under muscle paralysis.

Siesjö and Wieloch next tackle the fundamental topic of metabolic changes which underlie the features of brain ischaemia, including the oedema and the structural damage. They emphasize the deleterious effect of high blood glucose concentrations during partial brain ischaemia and in the recovery period since this leads to increased formation of brain lactacidosis. The resultant severe intracellular acidosis is thought to be a factor in ischaemic cell death. The accepted preoperative starvation regimen used clinically may therefore have more advantages than realized, and one might also infer that infusions of glucose should not be given before induced hypotension and that anaesthetics which increase blood glucose should be avoided.

There has been much progress in correlating changes in electrical function with varying degrees of flow deprivation, and Prior emphasizes the value of monitoring brain electrical function in high risk situations, especially since electrical failure precedes, and therefore forewarns of, structural damage. Indeed, in the Workshop it was argued that decreases in EEG power during induced hypotension can be accepted in the knowledge that the flow threshold for structural change is considerably lower than for electrical depression. However, in her paper Prior concludes "(decrease in EEG power) is a warning . . . and the patient is at risk of ischaemia and time is limited". The recent increase in clinical interest in evoked potential monitoring is put in the overall context of electrical monitoring in Prior's paper and the value of these techniques in the deeply sedated patient emphasized. In the Workshop discussion, the importance of maintaining a steady level of anaesthesia during intraoperative EEG or CFM monitoring was stressed.

Now that so much is known regarding brain ischaemia, can we effectively intervene therapeutically? Shapiro reviews the barbiturate situation and Gisvold and Steen survey other possible therapies. The Workshop discussed the general circulatory problems of high dose barbiturates and of calcium entry blockers, and the point was made that the maintenance of satisfactory systemic arterial pressure is probably at least as valuable as most forms of drug therapy. In a discussion of the choice of individual drugs, Shapiro recommended pentobarbitone for its pharmacokinetic profile and its lower fat solubility than thiopentone.

Finally two clinical areas in which brain ischaemia may be encountered—head injury and induced hypotension—were reviewed by Miller and McDowall, respectively. N. Branston, PH.D. (Gough-Cooper Department of Neurological Surgery, Institute of Neurology, The National Hospital, London WC1E 3BG) pointed out that subcortical changes may also be important in induced hypotension, for example in regional cortical ischaemia there is a loss of autoregulation in the thalamus. Siesjö agreed, and pointed to differences in responses to carbon dioxide and hypoglycaemia in the cerebellum and in the deep nuclei.

In the discussion of head injury, the influence of barbiturate therapy on the incidence of pulmonary infection and ARDS was raised, and Shapiro stated that his survey of the literature revealed no statistically significant increase in pulmonary infection in any one series, but that in most reports there was a non-statistically significant excess of pulmonary infections in barbiturate-treated patients.

D. G. McDowall

Br. J. Anaesth. (1985), **57**, 3–17

THE PATHOLOGY OF BRAIN ISCHAEMIA AND POSSIBILITIES FOR THERAPEUTIC INTERVENTION

D. I. GRAHAM

Irreversible hypoxic brain damage may occur as a consequence of such diverse conditions as lung and heart disease, shock, seizures or an episode of severe hypotension, and is a potential hazard to any patient undergoing general anaesthesia. The ultimate degree of neurological recovery may range from brain death and the vegetative state, to minor psychiatric disturbances and even apparent normality, and is determined by the severity of the initial stress and whether or not adequate resuscitation was commenced before brain damage became irreversible. Whatever the circumstances, irreversible hypoxic brain damage can occur whenever there is insufficient oxygen in blood or a reduced blood flow to the brain, or both. Brain oxygenation is dependent on respiration and the circulation, certain aspects of which should be considered before the pathology of hypoxic brain damage is described. The generic term "hypoxic" rather than "ischaemic" will be used, even though it is likely that much of this type of brain damage is produced by a reduction in cerebral perfusion.

Respiration

The oxygen content of blood decreases from 19.6 ml dl^{-1} to 12.9 ml dl^{-1} while passing through the brain and carbon dioxide content increases from 48.2 ml dl^{-1} in arterial blood to 54.8 ml dl^{-1} in the internal jugular vein. Thus the respiratory quotient to the brain is almost unity, implying that glucose is the most likely single source of energy by oxidation. In normal adult resting subjects, the cerebral metabolic rate for oxygen is 3.2–3.8 ml O_2 min^{-1}/100 g.

The effects of graded hypoxia on the brain have been studied recently by Salford, Plum and Seisjö (1973) and Salford, Plum and Brierley (1973), using a modified mechanically ventilated (Levine, 1960) preparation in the rat. A reduction in arterial $P\text{O}_2$ to 3.7 kPa for 30 min produced lactacidosis and a moderate change in energy state of brain tissue with minimal evidence of neuronal damage, whereas a reduction in arterial $P\text{O}_2$ to 2.8 kPa again for 30 min showed an abnormal energy state with persistent lactacidosis and more extensive brain damage. Using a similar model in the subhuman primate, Brierley and colleagues (1980) found that the arterial $P\text{O}_2$ could be reduced to 4.7 kPa without affecting either brain metabolism or function. It was not until arterial $P\text{O}_2$ had been reduced to 2.8–3.2 kPa for at least 8 min that the EEG became isoelectric and irreversible brain damage ensued.

Circulation

The brain of the normal adult receives approximately 15% of the cardiac output representing a mean cerebral flow of approximately 50 ml min^{-1}/100 g. The important relationship between perfusion pressure and cerebral blood flow is governed primarily by the phenomenon of autoregulation, which may be defined as the intrinsic tendency of the brain to maintain a relatively constant blood flow in response to moderate variations in perfusion pressure (Lassen, 1959; Harper, 1966). In man, cerebral blood flow remains constant within the pressure range of 65–140 mm Hg. The autoregulatory mechanism fails (the lower limit) below 65 mm Hg, when the vessels are dilated and flow then decreases with decreasing pressure. The brain compensates by increasing its extraction of oxygen so that the symptoms of cerebral ischaemia do not necessarily develop immediately. At high values of arterial pres-

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sure a point is reached where cerebral vasoconstriction cannot be sustained as cerebral blood flow increases; this is termed the upper limit of autoregulation. Factors that alter ability of the cerebral vessels to constrict or dilate interfere with autoregulation.

Cerebral blood flow depends upon two factors, namely the pressure difference between its arteries and veins (cerebral perfusion pressure) and the resistance of the intervening vessels (cerebrovascular resistance). For practical purposes, cerebral perfusion pressure is commonly regarded as the difference between systemic arterial pressure and intracranial pressure. The critical point is reached when intracranial pressure increases to approximately 45 mm Hg of systemic arterial pressure, following which cerebral blood flow decreases and the increasing intracranial pressure leads to a decrease in cerebral perfusion pressure. At low perfusion pressures, flow to the brain is patchy, as reflected in brain metabolism (Eklof and Śeisjö, 1972a, b, 1973; Welsh, O'Connor and Langfitt, 1977).

Energy is produced in the brain almost entirely by oxidative metabolism of glucose. The amount of glucose consumed is high (60 mg min^{-1}) reflecting inability of the brain, unlike other organs, to make use of complex substrates. Oxidative metabolism of glucose yields 38 molecules of ATP utilized in the synthesis of large molecules, transport mechanisms, the maintenance of membrane potentials and neurotransmitter metabolism.

Categories of Brain Hypoxia

Based upon the physiological considerations outlined above, these have been classified by Brierley (1976):

Stagnant hypoxia

(a) *Ischaemic.* This results from local or generalized arrest of cerebral blood flow.

Localized ischaemic damage occurs if blood flow through an artery or one of its branches is arrested. Thus, if the middle cerebral artery is occluded and there is no collateral circulation, a massive lesion results. Usually, however, there is some collateral circulation from the other major cerebral arteries and if this is sufficient to maintain viability of tissue, the infarct may be limited to basal ganglia and internal capsule.

Factors that influence the size of an infarct include the functional efficiency of the anastomotic vessels over the surface of the brain (Hutchinson and Yates, 1961), the configuration of the circle of Willis, which is of normal calibre and symmetrical in only 50% of adults (Alpers, Berry and Paddison, 1959) with an even higher incidence of variation in patients with post mortem evidence of cerebral infarction (Alpers and Berry, 1963), disease of the major neck arteries (Hutchinson and Yates, 1961) and the systemic arterial pressure. If all these are normal, the cortical lesion will be small, but if one or more is abnormal, the lesion will be larger. Cerebral infarction, therefore, rarely results from a single cause.

Generalized ischaemic brain damage occurs most commonly following cardiac arrest and is sometimes a complication of surgery under general anaesthesia at normal body temperature. Milstein (1956) estimated that cardiac arrest related to surgery was the cause of approximately 300 deaths per year in the United Kingdom but according to Wylie (1975), by 1970 the number of such deaths in England and Wales had decreased to 100 per annum. In patients who regain consciousness quickly after resuscitation, prognosis is good, with complete neurological recovery. However, if the cardiac arrest is of abrupt onset and occurs in a patient at normal body temperature, complete clinical recovery is unlikely if the period of arrest exceeds 5–7 min (Brierley, 1976), many of the patients dying within 24 h of the arrest (Bell and Hodgson, 1974; Willoughby and Leach, 1974). Although there appears to have been a reduction in the mortality following cardiac arrest, there does unfortunately appear to be an increasing number of patients who survive in a vegetative state (Brierley et al., 1971; Jennett and Plum, 1972). There is increasing awareness that, if the eventual outcome of patients in coma could be predicted accurately within hours of a cardiac arrest, resuscitative measures could be concentrated on patients in whom there was a reasonable chance of recovery. It has been suggested that periods of reduced cerebral perfusion pressure before or after a cardiac arrest may be as important as the duration of complete arrest (Miller and Meyers, 1972).

Attempts to arrest the cerebral circulation in normothermic experimental animals have been numerous and difficult to achieve, largely because of the brain's extensive and protective collateral circulation. Arrest of the cerebral circulation was achieved by Nemoto and colleagues (1977) in the Rhesus monkey, by a combination of an inflated cuff and drug-induced hypotension. It was concluded that the ischaemic threshold of the brain is approximately 15 min, a value similar to the 14–15 min threshold determined by Miller and Meyers (1970) and Marshall and colleagues (1975). In contrast to the traditional view that a complete revival without neurological or histological damage cannot be obtained after a complete cessation of brain circulation of more than approximately 7 min (Schneider, 1961; Brierley, 1976), it has been claimed that cerebral circulatory arrest of up to 60 min in the cat (Hossmann and Sato, 1970) and in Rhesus monkey (Hossmann and Zimmermann, 1974) can be associated with unequivocal signs of neuronal recovery. In these experiments, recovery of neuronal function comprised restoration of an abnormal EEG and the return of the pyramidal response; however, these criteria fall far short of recovery in a conventional clinical sense—no neurological deficit, normal EEG and resumption of spontaneous respiration (Brierley, 1980).

(b) *Oligaemia*. The brain or some portion of it receives a reduced blood supply.

A *localized* reduction of blood flow in a single cerebral artery or one of its branches results usually from a combination of systemic hypotension and narrowing of the vessel itself. It is thought to be a not uncommon cause of ischaemic brain damage and if the flow is impaired sufficiently, a localized area of tissue necrosis ensues.

Hypoxic brain damage may occur along the arterial boundary zones (watershed areas) of the cerebral and cerebellar hemispheres as a result of a rapid and considerable *generalized* reduction in cerebral perfusion pressure. Even though this pattern of damage had first been noted in 1937 by Wolf and Siris in four neurosurgical patients, it was not until some years later that the boundary zone pattern of ischaemic damage was attributed to a sudden decrease in arterial pressure (Zülch, 1953; Zülch and Behrend, 1961).

Experimental verification of the vulnerability of arterial boundary zones to hypotension was demonstrated by Brierley and Excell (1966), Brierley and colleagues (1969) and Meldrum and Brierley (1969). In these experiments, it was possible to show that, in the absence of hypoxaemia or a significant reduction of blood pH, ischaemic brain damage accentuated along the arterial boundary zones in primates could be induced by reducing the cerebral perfusion pressure to 3.3 kPa and maintaining an isoelectric EEG for at least 15 min. This pattern of brain damage has now been induced under various conditions that include the intracarotid injection of sufficient air (Brierley and Meldrum, 1974), in baboons with renovascular hypertension subjected to halothane-induced hypotension (Fitch et al., 1978) and in baboons using a combination of hypoxaemia (arterial $P\text{O}_2$ 2.9-3.3kPa) and carotid artery occlusion (Brierley et al., 1980).

This pattern of brain damage has been described in man after occlusion of one carotid artery (Romanul and Abramowicz, 1964), after dental anaesthesia in the semi-recumbent position (Brierley and Miller, 1966), after the over-zealous treatment of malignant hypertension by antihypertensive agents (Graham, 1975; Ledingham and Rajagopalan, 1979) and in the brains of patients dying from non-missile head injuries (Graham, Adams and Doyle, 1978). The particular vulnerability of the arterial boundary zones results from the anatomy of the vascular supply to the cortex of the cerebrum and cerebellum, blood being delivered through large vessels in the neck and ending in a system of small vessels that anastomose with their counterparts from adjacent arterial fields. Once the capacity for autoregulation of blood flow is lost as a result of a combination of reduced perfusion pressure and hypoxaemia, oxygenation decreases to a critical level in those parts of the arterial territory that are most remote from the parent stems, that is, in the boundary zones (Brierley, 1976).

Anoxic and hypoxic hypoxia

(a) *Anoxic*. This results from absence of oxygen in the lungs, which leads to hypoxaemia. Blood leaving the lungs may be devoid of oxygen in such diverse situations as space travel, complete obstruction of the respiratory tract above the tracheal bifurcation and drowning.

The physiological events have been studied in both man (Gastaut et al., 1961; Gastaut, Fischgold and Meyer, 1961; Ernsting, 1963) and experimental animals (Swann and Brucer, 1949; Snyder et al., 1979). It is evident from these studies that pure hypoxaemia is complicated by some degree of circulatory failure within that period of time and therefore cannot, *per se*, produce brain damage. If resuscitation is successful and brain damage is eventually proved, this must be ascribed to a combination of hypoxaemia and some reduction in cerebral blood flow. This combination is likely to lead to ischaemic changes along the arterial boundary zones. Thus, any delineation of purely anoxic brain damage is not as yet justified (Brierley, 1976).

(b) *Hypoxic*. This term implies some reduction in the oxygen tension of arterial blood from reduced oxygen content of inspired air, as may occur at high altitude, failure of pressurization in aircraft, inhalation of air mixed with inert gases during anaesthesia or impairment of pulmonary function.

Many attempts have been made to define a "critical" value of blood oxygenation below which brain damage will occur. In this sense Campbell (1965) considered 4.0 kPa to be the critical oxygen tension for arterial blood, while the corresponding value in brain venous blood has ranged from 2.3–2.5 kPa (Luft, 1965) to 1.6 kPa (Cohen, 1966). However, Gray and Horner (1970) showed that oxygen tensions as low as 1 kPa in arterial and 0.3 kPa in venous blood in man were compatible with survival without clinical evidence of brain damage. Indeed, Lübbers (1966) has shown that a local tissue oxygen tension of 0.13 kPa or less may be recorded in the brain of a normal experimental animal.

The importance of the cerebral circulation in conditions of hypoxia has been demonstrated recently in primates exposed to sub-atmospheric decompression (Nicholson and Ernsting, 1967; Brierley and Nicholson, 1969; Nicholson, Freeland and Brierley, 1970; Blagbrough, Brierley and Nicholson, 1973), in which model it was shown that brain damage was concentrated along the arterial boundary zones of the cortex of the cerebrum and cerebellum. Further work in a model of simulated decompression was achieved by Brierley and colleagues (1978) in lightly anaesthetized primates breathing spontaneously 3.2% oxygen (equivalent to an altitude of 37 500 feet). Again, ischaemic brain damage was accentuated along the arterial boundary zones. The pattern of brain damage in hypoxaemia, therefore, is indistinguishable from that seen after oligaemic hypoxia and this emphasizes the fact that systemic hypoxia can only produce brain damage secondary to depression of the myocardium and reduction in cerebral perfusion pressure. It should be noted, however, that the animals used in these various experiments were healthy, with normal systemic and cerebral vessels. In the human subject exposed to hypoxia, homeostatic mechanisms maintaining cerebral blood flow may be so restricted by hypertensive or occlusive cerebrovascular disorders, or both, that ischaemic damage may ensue.

Anaemic hypoxia

This results from reduced haemoglobin content, such as occurs in blood loss or anaemia. Poisoning by carbon monoxide, however, reduces the amount of circulating haemoglobin available to combine with oxygen and represents the only example of anaemic hypoxia that is apparently capable of producing hypoxic changes in the brain.

Histotoxic hypoxia

Poisoning of neuronal respiratory enzymes results in failure to utilize oxygen although the oxygen tension and content of arterial blood are normal.

Structural Changes Resulting from Hypoxia

The different susceptibility to hypoxia of the various cellular elements in the nervous system has been known for many years. According to Jacob (1963) "in general the nerve cells are the most sensitive followed by oligodendroglia and astrocytes, while the microglia and cellular elements of the vessels are the least vulnerable". Following an episode of hypoxia therefore, histological changes may be limited to nerve cells (selective neuronal necrosis) or may extend to involve glia and blood vessels (infarction).

The identification of neuronal changes unequivocally attributable to hypoxia is made difficult in the human brain because of frequent occurrence of histological artefact (Cammermeyer, 1961; Brown, 1977). This results partly from the autolysis that takes place between death and post-mortem, partly from slow penetration of the fixative in which the brain is immersed and partly from shortcomings in the processing of the tissue. Studies in various experimental animals and in selected human material have shown that there is an identifiable process, namely the *ischaemic cell process* that is the neuropathological common denominator in all types of hypoxia (Brown and Brierley, 1966; Brierley, Brown and Meldrum, 1971; Meldrum and Brierley, 1973). The time course of ischaemic cell change is relatively constant for nerve cells according to their size and site, so that the interval between a hypoxic episode and death, if between 2 and 24 h, can be assessed with reasonable accuracy. If a patient survives for more than 24–36 h, more advanced changes occur in nerve cells and early reactive changes appear in astrocytes, microglia and blood vessels. Reactive changes may be minimal. On the other hand, in an area of infarction, reactive changes become more intense, including the formation of lipid phagocytes. If survival is for more than a week or so, the damaged tissue becomes rarified from loss of myelin and there is a reactive astrocytosis. Collagen and reticulin fibres are laid down, dead tissue is removed and cystic spaces form, the walls of which comprise a gliomesodermal reaction.

The question of reversibility of the ischaemic cell process is of great clinical importance. From available information (Brown, 1977) it would seem likely that the greatly swollen mitochondria showing loss of cristae in the early stages of the ischaemic cell process are damaged irreversibly.

Neuropathology of Hypoxia

Stagnant hypoxia

Ischaemic—localized. If blood flow through an artery is arrested, an infarct develops within part or whole of the distribution of the occluded vessel. The arteries of the CNS have a fairly constant anatomical distribution, so that occlusion of the trunk or one or more of the larger branches produces a relatively constant neurological deficit. Usually the arterial occlusion results from atheroma or embolism; inflammatory disease, mechanical or surgical trauma are less common causes.

If the unfixed brain is sliced in the mortuary, it is impossible to recognize recent hypoxic brain damage. However, when the brain has been correctly dissected after adequate fixation, an infarct of approximately 18–24 h duration may just be recognizable, but even an experienced neuropathologist may fail to identify extensive diffuse hypoxic brain damage if it is less than some 3–4 day duration. An infarct may be haemorrhagic or anaemic (fig. 1); some swelling is common but, if sufficiently large, may constitute a space occupying mass within 24–48 h, resulting in tentorial herniation and secondary haemorrhage into the brain stem. The extent and severity of hypoxic brain damage can be identified and its duration analysed only by microscopic examination of many large bilateral and representative sections of the brain.

Ischaemic—generalized. If death occurs within 24–36 h of the arrest, the brain may appear normal externally and on section. Within 36–48 h it is some-

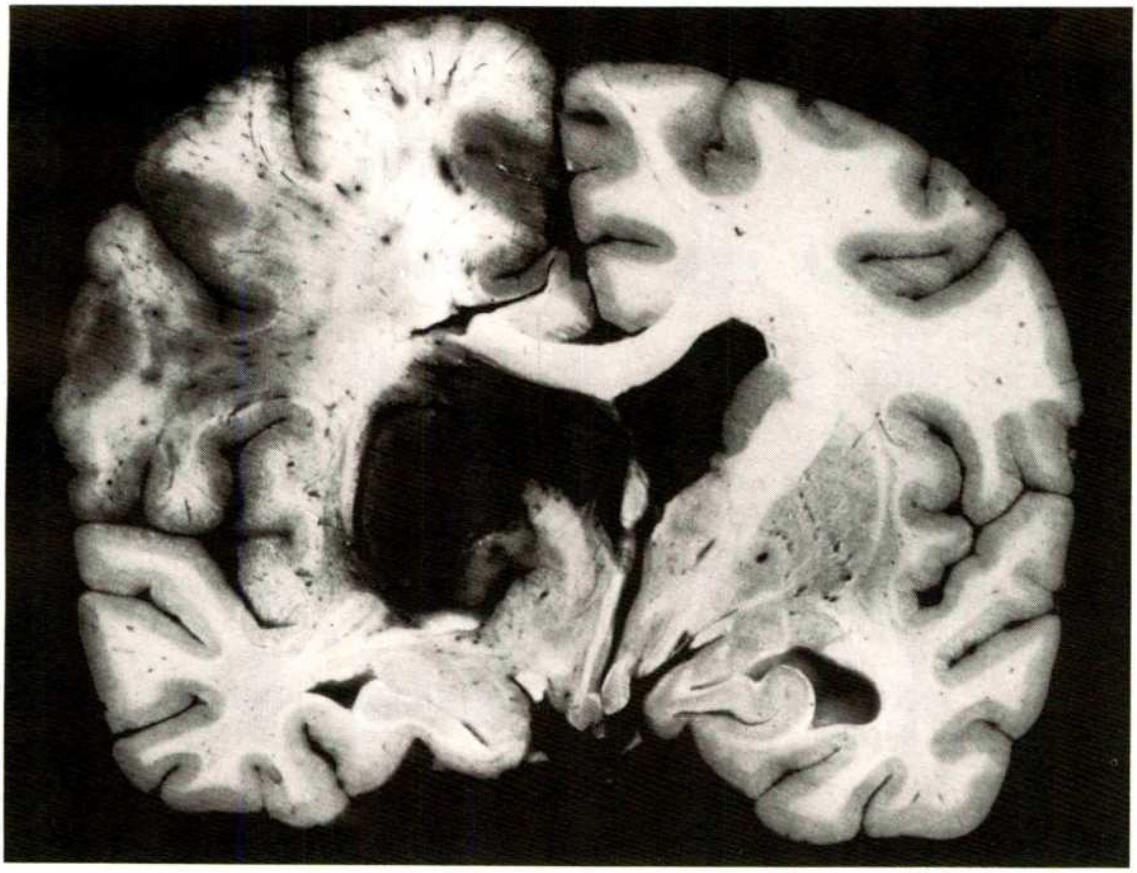

FIG. 1. Coronal section of brain from a patient who died 3 days after onset of "stroke". There is a swollen infarct in one cerebral hemisphere: the lesion is partly "anaemic" and partly "haemorrhagic".

times possible to identify laminar or patchy discolouration in the depth of sulci, particularly in the posterior halves of the cerebral hemispheres and selective necrosis in CA1 of Ammon's horn. Microscopy reveals diffuse neuronal necrosis with a characteristic pattern of selective vulnerability. Ischaemic damage is commonly greater within sulci than at the crests of gyri and is maximal in the 3rd, 5th and 6th layers of the parietal and occipital lobes (fig. 2). In Ammon's horn the CA1 sector is the most vulnerable (fig. 3) and these changes are sometimes associated with necrosis in the amygdaloid nucleus. The pattern of damage in the basal ganglia and thalamus is more variable. In the cerebellum, there is characteristically diffuse necrosis of Purkinje cells. Damage to the brain stem nuclei tends to be more severe in infants and young children than in adults. With increasing survival, there is an appreciable reduction in the weight of the brain resulting from atrophy and, on section, ventricular enlargement may be considerable (fig. 4). Whereas the cortex of the parietal and occipital lobes is reduced to a thin band of discoloured tissue, that of the frontal and temporal lobes may appear essentially normal. The hippocampi may show the features of Ammon's horn sclerosis.

Oligaemic

Oligaemic brain damage from systemic arterial hypotension conforms to one of three patterns (Adams et al., 1966), of which the first two types are the most common:

(1) Ischaemic damage is concentrated along the boundary zones in the arterial territories of the cortex and cerebellum (fig. 5) and is variable in the basal ganglia. If the lesions are large and of several days' duration, they may be recognized macroscopically, provided that the brain is cut in the coronal plane (fig. 6). They vary in size from foci of necrosis in the cortex to large wedge-shaped lesions extending from

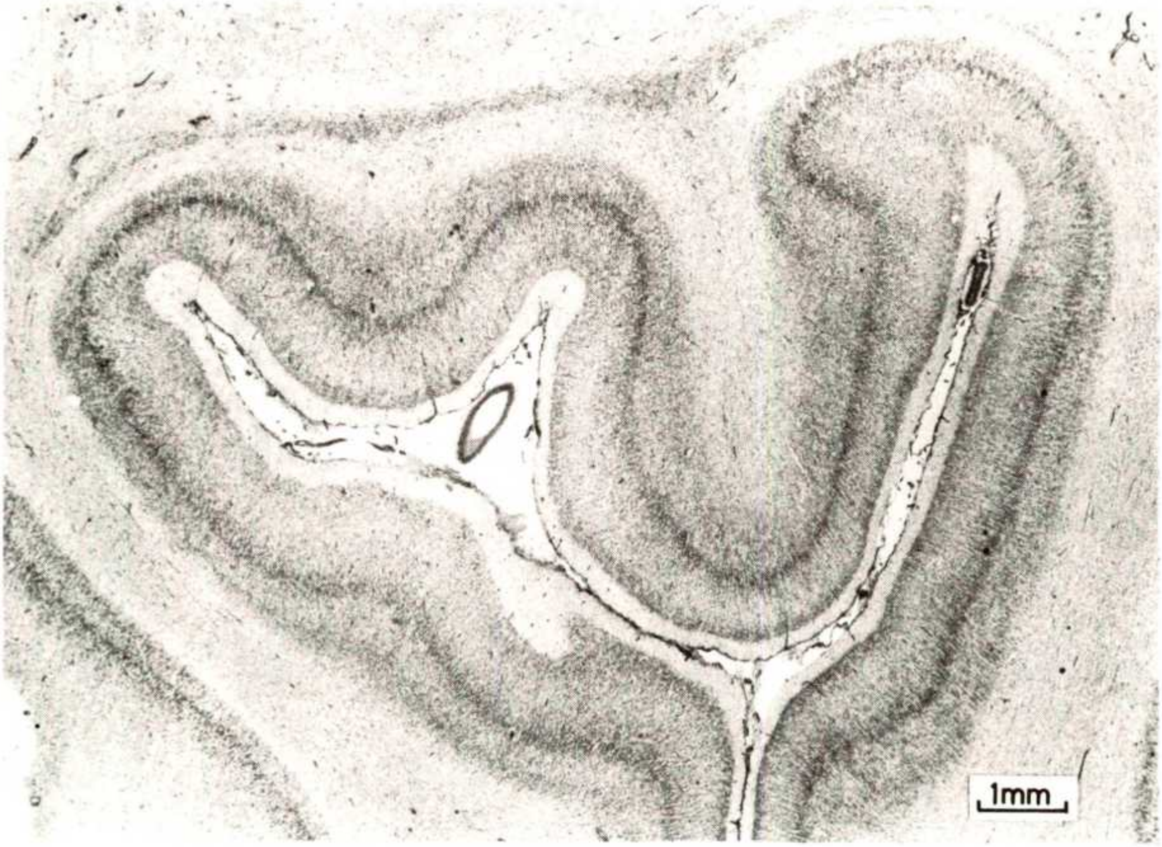

FIG. 2. Cortex in depths of sulcus. Note subtotal (laminar) necrosis of the third, fifth and sixth cortical layers (pallor of staining) with relative sparing of the second and fourth layers (darker staining). Cresyl violet.

the cortex almost to the angle of the lateral ventricle. Cortical damage is the most frequent and is most severe in the parieto–occipital regions, that is, in the common boundary zone between the territories of the anterior, middle and posterior cerebral arteries. Less commonly, there may be lesions between the middle and posterior cerebral arteries. The lesions are usually asymmetrical and may be unilateral. In the cerebellum, the boundary zone between the territories of the superior and posterior inferior cerebellar arteries lies just below the dorsal angle of each hemisphere. There is variable involvement of the basal ganglia and the Ammon's horn and brain stem are usually not involved.

On the basis of clinical evidence, this type of brain damage appears to be caused by a major and abrupt episode of hypotension, followed by rapid return to normal arterial pressure. It is often seen after a conscious patient has collapsed as a result of a sudden reduction in cardiac output resulting from ischaemic heart disease. It may occur in the anaesthetized subject during dental or neurosurgical procedures, particularly in the sitting position.

(2) Ischaemic damage is generalized in the cortex of the cerebrum and cerebellum, is minor or absent in the hippocampi and is often severe in the thalami. The number of reported patients is small (Brierley and Cooper, 1962; Adams et al., 1966), but it

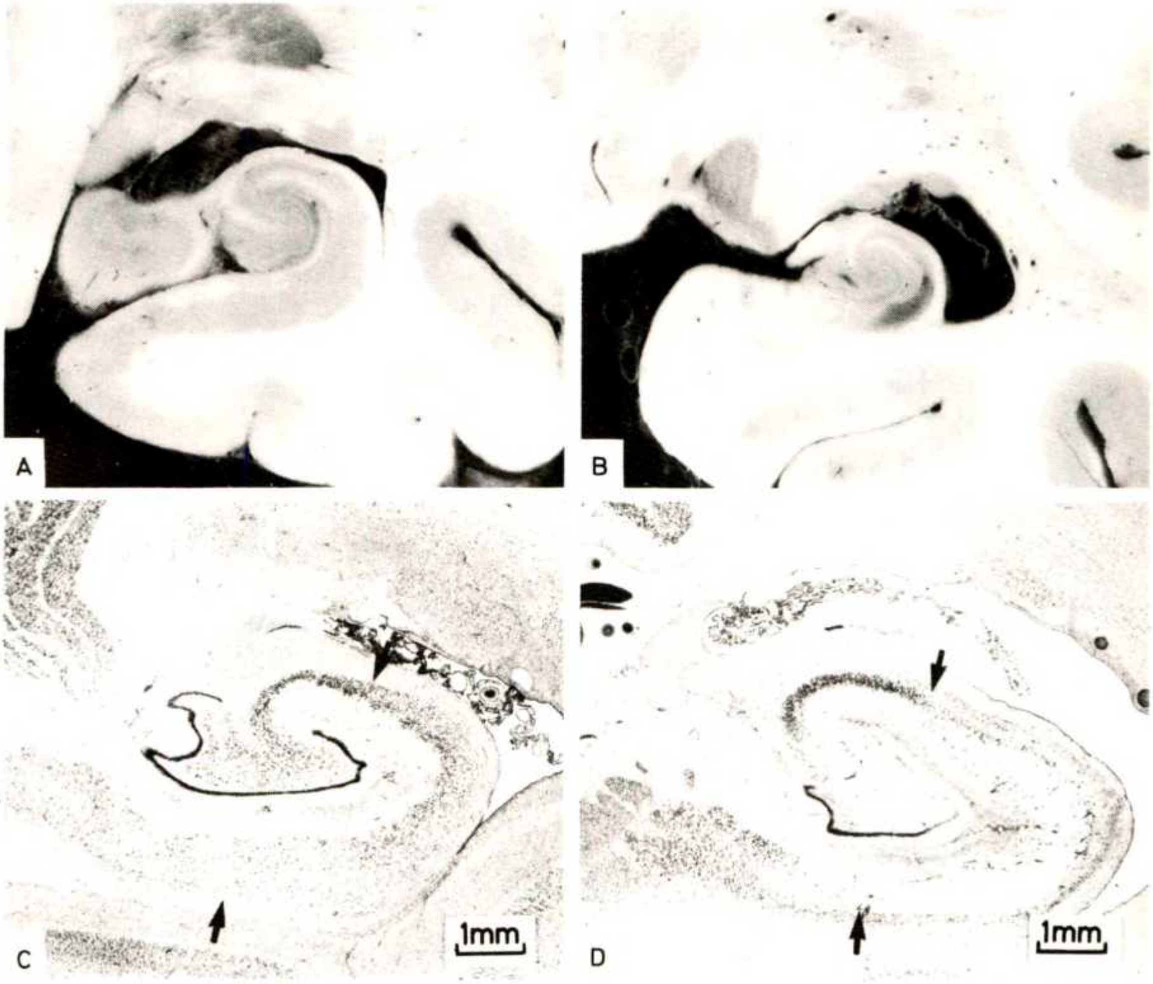

FIG. 3. A: Normal right Ammon's horn to compare with B. B: Right Ammon's horn. There is necrosis of CA1 (Sommer sector). C: Normal right Ammon's horn to compare with D: The arrows indicate CA1. Cresyl violet. D: Right Ammon's horn showing recent necrosis of CA1 (between arrows). Cresyl violet.

would seem that this type of damage appears to be associated with hypotension of a relatively slow onset but long duration.

(3) Ischaemic damage is generalized in the cortex of the cerebral and cerebellar hemispheres, but is variable, with accentuation along the arterial boundary zones. The hippocampi are usually spared and there is patchy damage in the basal ganglia. This type of damage appears to be associated with the abrupt onset of hypotension, which is responsible for the accentuation of damage in the boundary zones, followed by a sustained period of less severe hypotension which causes diffuse damage. Fortunately, such brain damage is rare after controlled drug-induced hypotension (McDowall, 1985).

Anoxic and hypoxic

According to Brierley (1976), these categories of hypoxia can produce brain damage only through the medium of a secondary depression of the myocardium, the pattern of damage being similar to that of oligaemic hypoxic brain damage described above.

Selective vulnerability

In its most classical form, this is seen after an episode of global ischaemia, *viz*. cardiorespiratory arrest (see above). While it is accepted that the more recently evolved regions of the brain are most vulnerable to hypoxia, damage is never total and even in patients in the vegetative state there may be large numbers of normal nerve cells.

Two major hypotheses have been advanced to explain the characteristic distribution of hypoxic brain damage. That advanced by Spielmeyer (1925) is known as the vascular theory and invokes anatomical factors such as the length and course of a particular artery, in addition to physiological factors, as a basis for local vulnerability. The other hypothesis, known as the concept of pathoclisis of

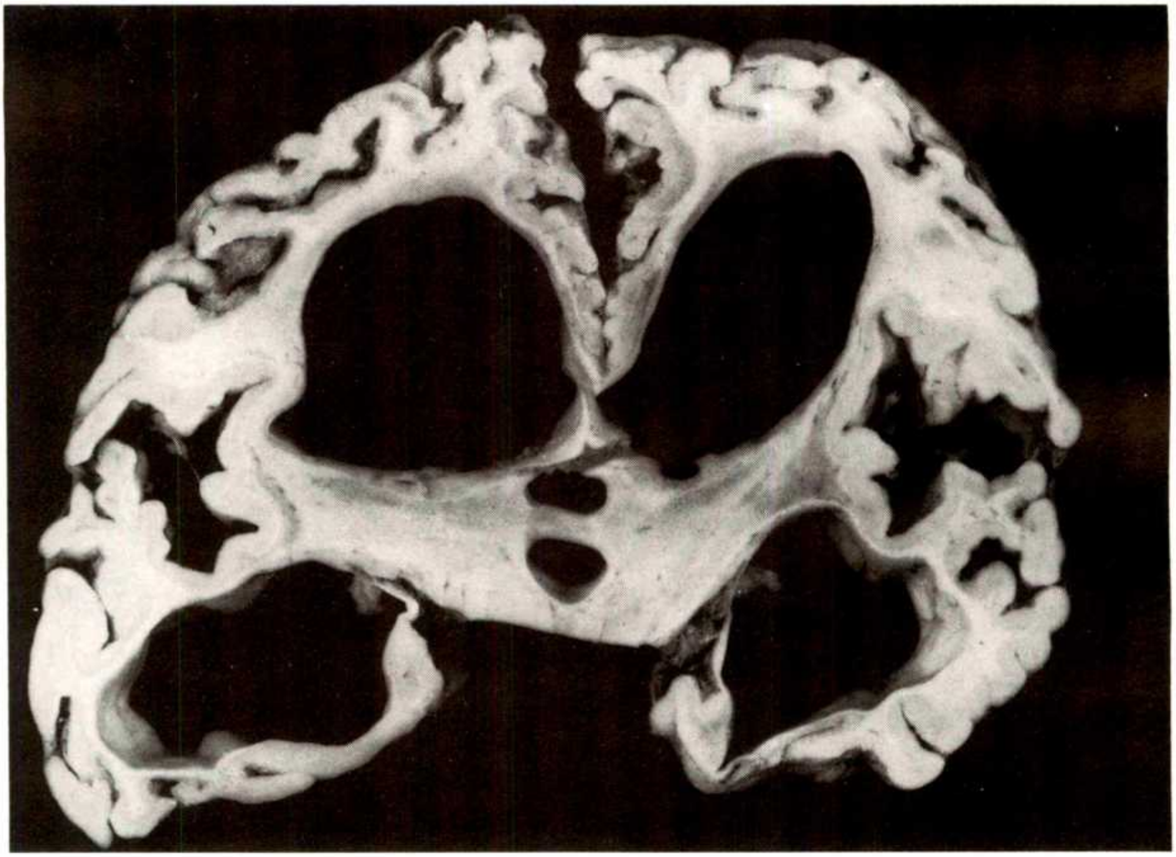

FIG. 4. Coronal section of brain from patient who survived 4 years in a vegetative state after a cardiac arrest. There is considerable narrowing of the cortex, loss of deep white matter and gross enlargement of the ventricles. The Ammon's horns and the thalami are also small.

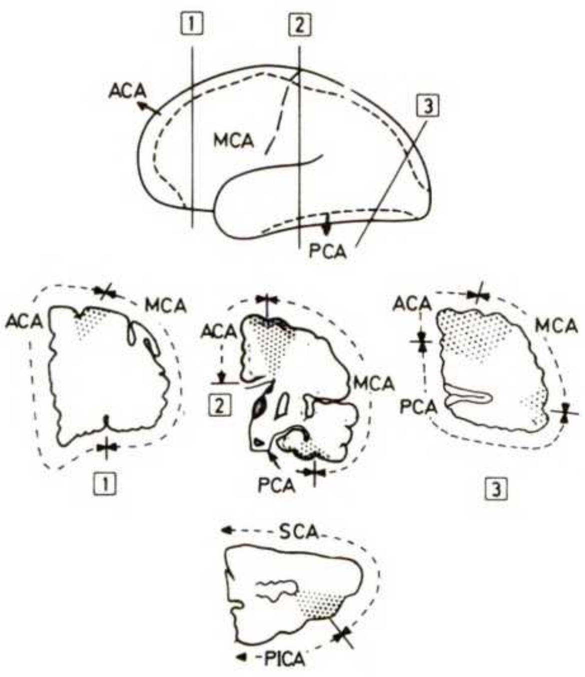

FIG. 5. Diagram to show arterial boundary zones in cerebral and cerebellar hemispheres. The right cerebral hemisphere is shown at three levels, *viz.* 1 = frontal, 2 = mid-temporal and 3 = occipital. Each boundary zone is stippled. ACA = anterior cerebral artery, MCA = middle cerebral artery, PCA = posterior cerebral artery, SCA = superior cerebellar artery and PICA = posterior inferior cerebellar artery.

C. and O. Vogt (1937), postulated particular physico–chemical properties as a basis for vulnerability. The arguments for and against the vascular theory have been reviewed by Scholz (1963) but, even in the hippocampus, it is difficult to explain the pattern of involvement from anatomical vascular factors alone. Observations in support of the theory of pathoclisis include the demonstration of a high concentration of zinc in certain zones of the hippocampus (Maske, 1955; Friede, 1966) and the partial or complete loss of nerve cells in the zinc-rich zones following a single dose of 3-acetyl pyridine (Coggeshall and MacLean, 1958). Support for the theory has also been provided by Kato and Lowry (1973), who found large differences in the enzyme patterns of cell bodies of different neuronal populations using quantitive microchemical techniques. However, it has been difficult to relate these findings to known patterns of vulnerability, although irreversible brain damage has been attributed in these areas to concentrations of brain lactic acid in excess of 20 mmol kg^{-1} (Myers, 1979; Rehncrona, Rosen and Siesjö, 1980, 1981). Lactacidosis, however, is not an invariable accompaniment of the various categories of hypoxia and therefore cannot qualify as a major determinant of cell damage and selective vulnerability.

In the search for a common mechanism of cell damage, increasing attention has been paid to events of a potentially harmful nature occurring in the period of recirculation/reoxygenation (Siesjö, 1981). During this period there is undoubted abnormal ion homeostasis and so a working hypothesis has been developed, suggesting that an altered calcium homeostasis with associated activation of phospholipases and an accumulation of free fatty acids may provide a mechanism for cell damage (Siesjö, 1981; Raichle, 1983).

A number of studies have shown that neuronal injury indistinguishable from the ischaemic cell process can be induced in susceptible nerve cells by excessively enhanced neuronal activity. For example, selective involvement of the hippocampus is found commonly in most categories of cerebral hypoxia and after status epilepticus. In the latter situation, as the seizure activity augments cerebral energy consumption, a failure of energy supply to keep pace with energy utilization would seem likely to be the important factor contributing to neuronal damage; a mis-matching of local metabolism and blood flow may therefore be a pathogenetic factor. Support for this hypothesis has been provided recently in studies using kainic acid as a convulsant (Lothman and Collins, 1981), when a marked increase in the measured rate of glucose utilization in discrete areas of the limbic system were not accompanied by significant changes in local blood flow.

The occurrence of metabolic failure and calcium accumulation in the genesis of hypoxic brain damage has been discussed recently by Meldrum (1983), who has suggested that selectively vulnerable neurones in all categories of hypoxia, and in hypoglycaemia, are those in which the entry of calcium is favoured by neuronal depolarization or by bursting behaviour during a restitution phase in hypoxia or ischaemia. It is suggested that, in the selectively vulnerable areas, the capacity of the nerve cells to sequester or extrude calcium is exceeded. Mitochondria swell, calcium is not released into the cytoplasm and the ischaemic cell process is initiated (Siesjö and Wieloch, 1985).

Possibilities for Therapeutic Intervention

The function and structural integrity of the brain are related closely to its blood supply. It therefore fol-

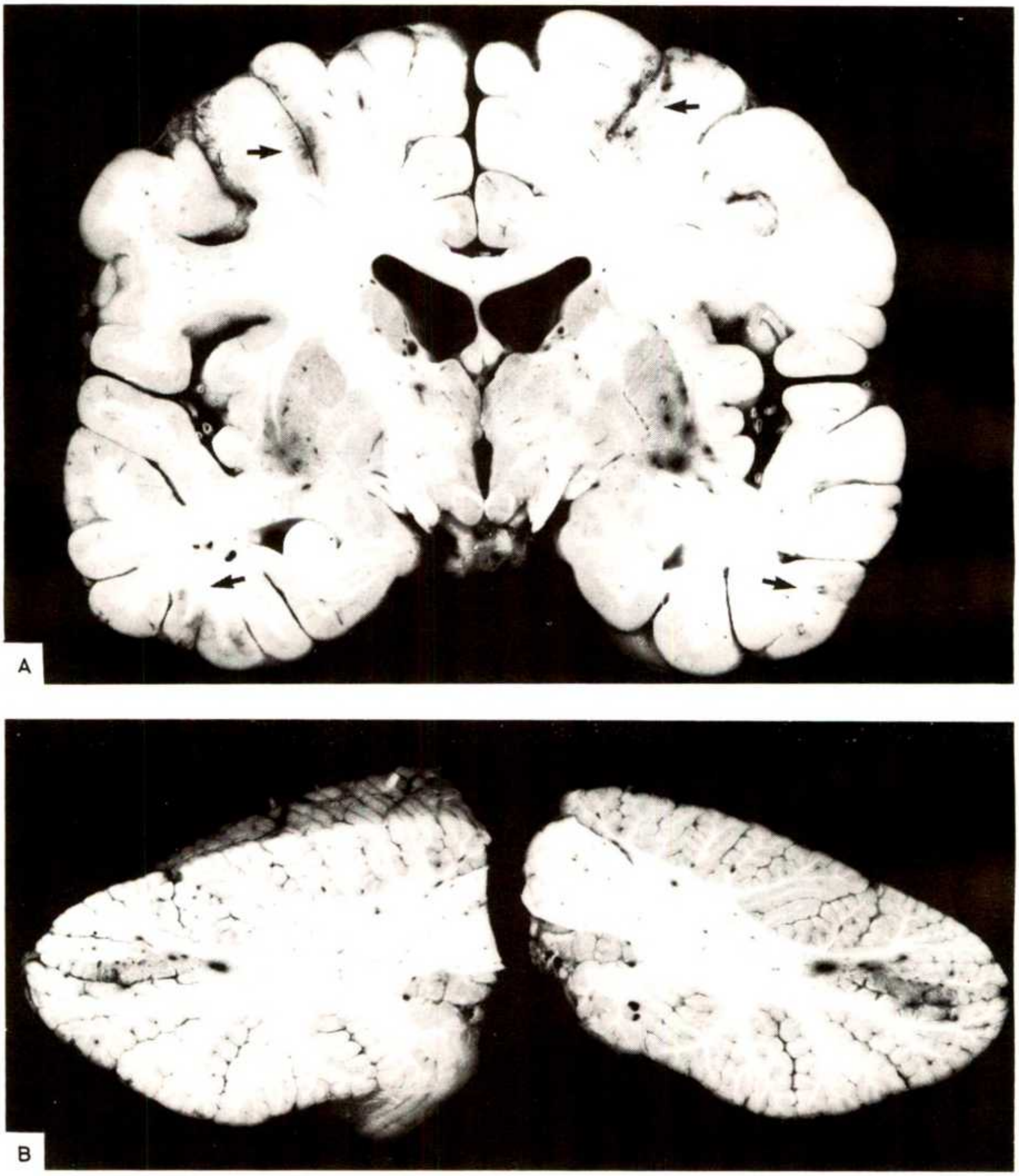

FIG. 6. A: Coronal section of brain from patient who survived 17 days after a myocardial infarct. Note focally haemorrhagic infarcts (arrows) in the boundary zones between the anterior and middle cerebral arterial territories, and between the middle and posterior cerebral arterial territories. Compare with figure 5. B: Same patient as in A: Slices of cerebellar hemispheres to show focally haemorrhagic infarction at dorsal angle of each hemisphere, that is in the boundary zones between the superior and posterior inferior cerebellar arterial territories. Compare with figure 5.

lows that, given an adequate supply of oxygenated blood, the brain will be protected from the adverse effects of hypoxia. However, most patients with hypoxic brain damage are first seen only after the signs and symptoms of irreversible damage have already developed. It is not surprising, therefore, that considerable emphasis has been placed on its prevention as cerebrovascular disorders continue to be a major health problem in the western hemisphere. For example, according to Wolf and Kannel (1982), in the U.S.A. there are some 500 000 new patients with stroke each year, about half of whom die. Stroke accounts for some 10% of all deaths and in those who survive approximately 15% are severely disabled, only 10% returning to normal activity (Gresham et al., 1979). Approximately 85% of these strokes result from cerebral infarction.

A number of pre-morbid factors presaging stroke have been identified, the most important being the development of atheroma, hypertension, heart disease and diabetes mellitus. There is evidence from several countries that the incidence of stroke is now declining (Levy, 1979). This appears at least in part to result from more effective treatment of hypertension (Veterans Administration Co-Operative Study Group, 1967, 1970; Hypertension Detection and Follow-up Program Co-Operative Group, 1979a, b). It therefore seems likely that the prompt and adequate treatment of hypertension, together with the encouragement of other preventative health measures including the avoidance of obesity and of cigarette smoking, will greatly reduce the incidence of stroke. By identifying various hazards and estimating the degree of risk, it should be possible to screen the population in order to identify a stroke risk profile in the pre-symptomatic stage.

Protection of hypoxic brain damage

The outcome of *focal* ischaemia depends in large measure on the residual blood flow through the ischaemic area (Symon, 1985), while the outcome after global arrest depends on the duration of the ischaemia and the relationship between ischaemic membrane failure and the subsequent development of irreversible damage (Astrup, 1982; Wiedemann and Hoyer, 1983.

According to Hossmann (1982), there are two main ways by which hypoxic brain damage may be ameliorated. First, by the overall inhibition of metabolic activity in order to reduce the oxygen and substrate requirements of the brain, and second by improving mitochondrial efficiency in order to optimize energy output in the presence of a reduced oxygen supply. The conditions that are presently known to delay the development of membrane failure, their mode of action and role in protection have recently been reviewed (Astrup, 1982; Hossmann, 1982). A most efficient procedure for inhibiting metabolic activity is hypothermia, as is well known from clinical experience in the fields of cardiac surgery and neurosurgery. Another approach for inhibiting metabolic activity of the brain is in the use of barbiturates and non-barbiturate drugs (Gisvold and Steen, 1985; Shapiro, 1985). The literature is extensive, these agents having been given before and after the onset of ischaemia both to man and to various experimental animals. A further recent development is the use of so-called anti-anoxic drugs which improve mitochondrial efficiency.

Complications of hypoxic brain damage

Treatment of ischaemic brain oedema. There is increasing evidence that brain swelling plays an important role in the pathophysiology of "stroke" (Katzman et al., 1977) and that there are two forms of hypoxic oedema—an early cytotoxic type and a delayed vasogenic type (Klatzo, 1985). After the i.v. injection of Evans blue, it was found that the leakage of proteins across the blood–brain barrier was a relatively late event occurring only hours or days after the onset of cerebral infarction (Klatzo, 1967). This accorded with clinical evidence that death from increased intracranial pressure with tentorial herniation as a result of cerebral infarction is maximal some 2–4 day after the onset of the ischaemic event (Bounds et al., 1981).

More recent studies, however, have shown that there is dysfunction of the blood–brain barrier relatively soon after an episode of cerebral hypoxia. For example, following a period of circulatory arrest, Hossmann (1976, 1977) showed that, if reperfusion was established at a high systemic arterial pressure, severe cytotoxic brain oedema developed as a result of imbalance between osmotic and ionic homeostasis between the intra- and extracellular compartments of the brain. When an ischaemic brain is recirculated with blood there is a sudden increase in brain volume and an increase in intracranial pressure. Energy-producing metabolism, however, is restored rapidly, tissue osmolality decreases and energy-dependent ion-exchange pumps are re-activated with the resolution of the post-ischaemic oedema.

In focal ischaemia, oedema is initially of the cytotoxic type. This again results from an increase in tissue osmolality and a disturbance of ion homeostasis. Unlike global ischaemia where oedema develops only during the recirculation phase, oedema formation in focal ischaemia develops during the ischaemic process because collateral blood flow provides a continuous supply of fluid and electrolytes to the ischaemic tissue. Eventually, a vasogenic type of oedema develops in which there is leakage of serum proteins across the blood–brain barrier. Recent experimental studies have shown that there is dysfunction of the blood–brain barrier immediately following cerebral infarction (Petito, 1979) and that the extent and severity of the increased permeability correlates with the severity of ischaemic damage. In these studies it was found that, at least initially, oedema formation did not result from breakdown *per se* of the blood–brain barrier, but rather from enhanced micropinocytosis, the inter-endothelial junctions always remaining tight. In further studies, Petito and colleagues (1982) confirmed the earlier observations of Plum, Posner and Alvord (1963) that cerebral ischaemia produces sustained oedema and increased permeability of the blood–brain barrier only after tissue has undergone infarction.

Following 30–90 min of ischaemia in the primate cerebral cortex, Symon, Branston and Chikovani (1979) found a significant increase in water content in areas in which blood flow was reduced to less than 20 ml min^{-1}/100 g. In the cat model of middle cerebral artery occlusion, Schuier and Hossmann (1980) found that brain oedema developed when cerebral blood flow decreased to less than 10–15 ml min^{-1}/100 g. A further potential complication of re-establishing flow in an already ischaemic area is that the reperfusion may convert a non-haemorrhagic infarct into a haemorrhagic lesion (Kamijyo, Garcia and Cooper, 1977).

The cytotoxic type of oedema can be treated by osmotherapy using agents such as glycerol and mannitol, whereas treatment of the late vasogenic type of oedema has been attempted using steroids (Hossmann, 1982; Klatzo, 1985).

Treatment of seizures. Seizures are said to develop in 10–30% of patients with focal cerebral ischaemia (Cocito, Favale and Reni, 1982) with a higher incidence of 30% after cardiorespiratory arrest (Prior, 1973). Even though focal seizures may be important, the development of status epilepticus is likely to be more serious, adding further injury to an already damaged brain. Indeed, it has been shown in the experimental animal (Meldrum, 1983) that prolonged seizures lead to a pattern of hypoxic brain damage that is very similar to that found in man after status epilepticus (Meyer, Beck and Shepherd, 1955). Such seizures are associated with various systemic changes that include hyperpyrexia, lactacidosis, arterial hypotension, hypoxaemia and sometimes hypoglycaemia.

CONCLUSIONS

Hypoxic brain damage may occur in diverse clinical situations where there is an inadequate supply of oxygen or blood to the nerve cells. If a patient dies within a few hours of such an episode, the pathologist may be unable to identify any macroscopic abnormalities in the brain. Varying degrees of damage, however, are identified easily with longer survival if the brain has been dissected correctly after adequate fixation. The identification of early hypoxic brain damage is difficult in the human brain because of histological artefact. Nevertheless, it is usually possible to establish that a patient has experienced an episode of hypoxia sufficiently severe to produce widespread damage by histological examination of the selectively vulnerable areas.

Complete recovery in patients with transient ischaemic attacks and the frequent good recovery in more severe ischaemic strokes have given clinical credence to the concept of the ischaemic penumbra. Thus, increasing attention has been paid to those factors that influence the cerebral circulation and may prevent infarction and induce full recovery. Of critical importance for protection in both focal and global ischaemia is the prevention or delay in the development of membrane failure. In focal ischaemia, membrane failure can be prevented by maintaining local blood flow above the flow threshold of membrane failure. In complete global ischaemia, the development of membrane failure can, at the most, be delayed.

With a better understanding of the pathophysiology of hypoxic brain damage, it is now clear that a variety of factors initiated by the hypoxic event contribute to further tissue damage. These include an increase in the extracellular fluid potassium concentration, the release of neurotransmitters, and the liberation of vaso-active substances capable of disrupting blood flow in relation to the metabolic needs of the tissue. Either singly or in combination, such events may initiate seizures and cause the ischaemic tissue to swell—complications which, in turn, add further damage to the already ischaemic brain.

There is increasing evidence that a disturbance in calcium homeostasis is the final common pathway by which cells die. The exact events that lead up to this derangement are not clear, but within the nervous system it may result from burst firing, an electrophysiological event that appears to correspond with the known pattern of selective vulnerability of the brain to hypoxia.

It seems possible that, regardless of its cause, hypoxic brain tissue may be protected by treatments that either prevent or delay the development of membrane failure. It should be noted, however, that although the ability to protect the brain from hypoxia may be of considerable value in cardiac surgery and neurosurgery (Miller, 1985), it is likely that such measures are unlikely to be efficacious for the majority of patients who develop ischaemic "strokes" at home. Hence, increasing attention is being paid to the identification of patients at risk, so that appropriate preventative measures can be instigated.

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Br. J. Anaesth. (1985), 57, 18–22

BRAIN OEDEMA FOLLOWING BRAIN ISCHAEMIA AND THE INFLUENCE OF THERAPY

I. KLATZO

Brain oedema has been defined as *an abnormal accumulation of fluid within the brain parenchyma associated with a volumetric enlargement of the brain tissue*. According to this definition, neither a volumetric enlargement from an increased blood volume alone, without an increase in parenchymatous fluid, nor a mere shift of water from extracellular into intracellular compartment will constitute brain oedema.

At the present time, brain oedema is classified into two types: *cytotoxic* and *vasogenic* (Klatzo, 1967) in accordance with two basically different pathological mechanisms involved, each characterized by distinctly different profiles of concurrent changes.

In most instances, the labelling of oedema as vasogenic or cytotoxic is only relative, since it is exceptional that only one of the two mechanisms would be operating exclusively. However, an understanding of the nature and dynamics of various brain disorders, associated with oedema, should be enhanced considerably by recognition of relative involvement of these two basic types of oedema in various phases of a pathological process.

Vasogenic brain oedema (VBO)

The main pathogenic event is *an increase in cerebrovascular permeability associated with the leakage of serum proteins into the brain parenchyma.* This constitutes an essential event in the development and dynamics of this type of oedema.

The close interrelationship between extravasation of serum proteins and vasogenic oedema has been established in several studies. In the experimental model of cold injury, mapping out the water content of various regions of the brain by measuring the specific gravity of 1-mm diameter tissue samples (fig. 1), a close correlation between water content and the extravasated serum proteins, demonstrated by an immunocytochemical procedure, was apparent, especially in the stages of resolution of oedema (Klatzo et al., 1980). In a more recent study by Kuroiwa and others (1984), a quantitative, direct correlation was shown between amounts of extravasated protein and increments in water content. A temporary leakage of the blood–brain barrier (BBB) to proteins was produced under experimental conditions in which no recognizable injury to cellular elements of brain parenchyma could be seen. In these studies it was significant that progressive decrease in protein and water content followed the closure of the barrier to proteins and not to micromolecular substances such as sodium fluorescein tracer, which leaked for much longer. This observation suggests that electrolytes and water can move rather easily in and out of brain parenchyma, and it is retention of water by the presence of extracellular proteins which is the most essential factor in formation and persistence of the vasogenic type of oedema.

In an interpretation of the dynamics of the VBO, as produced in cold injury, the Starling equation concerning the fluid flow from the blood into the tissue: $J\text{v (flow)} = Lp\ [(P^{\text{plasma}} - P^{\text{tissue}}) - \sigma(\Pi^{\text{plasma}} - \Pi^{\text{tissue}})]$ seems to be applicable to different phases of the process. Thus, in the initial phases of oedema development, in the zone of increased cerebrovascular permeability, the Lp (hydrolic conductivity of endothelial membrane) and the intravascular hydrostatic pressure (P^{plasma}) appear to be predominant forces in the spread of oedema. The effect of hydrostatic pressure on the dynamics of VBO was demonstrated clearly by Klatzo and others (1967) in their observations on dynamics of cold injury oedema. On the other hand, in the oedematous

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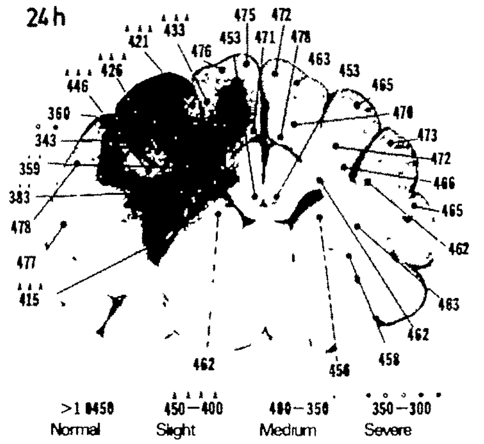

FIG 1 Twenty-four-hour-old cold lesion in the cat. The Evans Blue discoloration outlines preferential spreading of oedema in the white matter. The numbers point to the location of 1-mm diameter samples in the brain tissue. The specific gravity values less than 1.0450 are classified arbitrarily into slight, medium and severe degrees of oedema intensity. The measurements show a gradient in intensity of oedema diminishing from the site of cryogenic injury. A slight oedema is also present in the cerebral cortex of the injured gyrus and of the immediately adjacent portions of the neighbouring gyri. (From: Klatzo et al., 1984.)

white matter, where the BBB to proteins remains intact, the Lp and σ (osmotic reflection coefficient) remain as in the normal brain tissue and the flow of fluid (Jv) across the vascular wall becomes influenced by the difference in osmotic pressures between plasma (Π^{plasma}) and oedematous tissue (Π^{tissue}). Since the preserved BBB impedes the re-entry of extravasated proteins into the vascular lumen, the proteins are trapped for some time in the extracellular spaces, exerting their colloidal-osmotic pressure and retarding the movement of water into the vessels. In this respect, the osmotic pressure of proteins (which is considered to be rather low) may increase considerably in the area of oedema by fractionation into various smaller units (Rasmussen and Klatzo, 1969); also, a significant water binding capacity of proteins was reported in the recent studies on free and bound water in various brain disorders (Furuse et al., 1984; Kuchiwaki et al., 1984).

From the sites of increased cerebrovascular permeability, oedema fluid overcomes resistance of cellular structures of the brain tissue and spreads by bulk flow propelled by hydrostatic forces. This results in increasing interstitial fluid pressure and the development of pressure gradients which determine the driving force of the oedema fluid. As the resistance of the tissue is overcome, there is initially a rather steep increase in interstitial tissue pressure required to separate densely packed cellular structures and thus dilate the extracellular spaces. This may provide a "safety factor" in protecting the brain tissue from oedema of lesser intensity (Reulen et al., 1976). The preferential spread of VBO through the white matter is related presumably to the structural features of the tissue. Ultrastructurally, the grey matter resembles a dense jungle of tangled cellular structures, whereas the white matter consists of rather straight and orderly arrangement of extracellular channels, thus providing less resistance to the flow of oedema fluid.

Theoretically, the clearance of vasogenic oedema fluid may proceed by several routes: CSF, blood or lymphatic channels (Marmarou et al., 1984). Reulen and colleagues (1976) postulated that oedema fluid follows a downhill pressure gradient and it is cleared through the ventricular wall into the CSF. Klatzo and others (1980) indicated that intracellular uptake of serum proteins by the glial elements may constitute a major mechanism for resolution of VBO. In their quantitative studies, Marmarou and others (1984) examined the relative involvement of various routes and concluded that the clearance of oedema by bulk flow into the CSF is restricted to the early phase of the oedema and, following this stage, the loss of water from the tissue is associated closely with the dynamics of protein clearance. These studies also indicated that the clearance by the vascular route was considerably less than by CSF, whereas the lymphatic route proved to be rather insignificant.

Cytotoxic brain oedema (CBO)

The main event is ***the swelling of cellular elements of brain parenchyma by the effect of some cytotoxic agents*** which may selectively affect various cellular types and structures. The most common CBO occurs in hypoxic and ischaemic conditions and is related to interference with cellular osmoregulation which relies on energy-dependent function of ionic pumps. Other forms of CBO related to various toxic agents have been described, such as that caused by triethyltin and hexachlorophene intoxication producing splitting of the intraperiod line of myelin sheaths and accumulation of water in intramyelinic clefts (Aleu, Katzman and Terry, 1963); hydrogen cyanide intoxication resulting in selective swelling of (predominantly) axons (Hirano, Levine and Zimmerman, 1967); and by kainic acid which may produce a selective swelling of astrocytes (Seitelberger et al., 1984). The BBB permeability to serum proteins in a pure form of CBO remains basically intact, whereas an increased entry of water into brain parenchyma is related primarily to osmotic gradients which develop from interference with cellular osmoregulation.

Pathophysiology of ischaemic injury

As noted above, ischaemic brain oedema (IBO) *has elements of both VBO and CBO* and the assessment of their relative involvement is important in the elucidation of the pathophysiology of ischaemic injury.

Cytotoxic intracellular accumulation of water dominates the initial stages of IBO and it is related to an acute tissue deprivation of glucose and oxygen. The main event here is a disturbance of cellular osmoregulation, which depends primarily on the Na^+–K^+ exchange pump, with ATP as the energy source. In global ischaemia, with total cessation of blood flow and before recirculation, there is no oedema (which, according to definition, must be associated with a volumetric increase of tissue), since the ischaemic swelling of cellular elements is related merely to the shift of water from extra- to intracellular compartment and because only the systemic circulation may provide water for a net volumetric increase.

In the regional ischaemia produced by occlusion of a major artery, the increase in water content of the tissue may be demonstrated within 5 min, using the sensitive gravimetric method (Fujimoto et al., 1976); otherwise, electrical impedance measurements indicate, within a few minutes, reduction of extracellular spaces by cellular swelling. Generally, the vulnerability of brain tissue to ischaemia is related to discrepancy between energy demand and supply. Thus, the grey matter appears to be more sensitive to ischaemic injury than the white matter and the cytotoxic oedema is initially more pronounced in grey than white matter.

In recent years, concepts of thresholds and of selective vulnerability proved useful in the interpretation of some aspects of the pathophysiology of cerebral ischaemia. Thus, it was shown that the onset of cytotoxicity occurs at a certain threshold of cerebral blood flow (CBF) reduction (<20 ml $min^{-1}/100$ g) (Symon, Branston and Chikovani, 1979) and the recent observations on selective vulnerability indicate that the thresholds to ischaemic injury vary in different brain regions. Thus, at similar values of reduction in CBF, certain regions develop severe ischaemic injury and oedema, whereas the other regions do not (Klatzo, 1984). Also, differences in ischaemic injury and oedema appear to be age-dependent, as has been noted in most recent comparative studies on effects of ischaemia in 3-week-old and adult gerbils (Martinez et al., 1984).

The opening of the BBB to proteins in cerebral ischaemia introduces the element of VBO. This may occur in two separate phases following release of arterial occlusion (Kuroiwa et al., 1982). The first opening of the BBB does occur promptly after release of occlusion when, during the ischaemia, the CBF reduction is below certain threshold values. This is followed by an acute reactive hyperaemia, which induces a barrier opening by the haemodynamic effect of greatly increased intraluminal pressure in blood vessels, maximally dilated as a result of loss of autoregulation. The important factors in this haemodynamic opening are the intensity of preceding ischaemia and the amplitude and rapidity in the development of reactive hyperaemia.

The second opening of the BBB occurs after considerable delay (Suzuki et al., 1983), and it appears to be related clearly to factors deriving from the severely damaged ischaemic tissue. The breakdown of the BBB to proteins in the permanent arterial occlusion is of a similar nature and this takes place usually after some hours in instances when the intensity of ischaemia is below certain threshold values (<12 ml $min^{-1}/100$ g) (Wagner et al., 1983).

The leakage of serum proteins into brain tissue undoubtedly aggravates the existing cytotoxic oedema. It was shown (Klatzo et al., 1984) that areas with protein extravasation reveal, as a rule, a significantly higher water increase than areas with cytotoxic oedema. With further progression of ischaemic injury and onset of necrotic changes, the extracellular compartment enlarges rapidly as a result of rupture of membranes of dying cells, the contents of which are spilled out into extracellular spaces. All this leads to a considerable increase in osmolality by accumulation of catabolic products of cellular disintegration and a further significant increase in water content. In such severely injured oedematous foci, the resulting marked increase in tissue pressure affects significantly the surrounding regions of penumbra, where it is likely to produce depression of regional blood flow below the critical thresholds of viability and to a further extension of territory with an irreversible tissue damage (fig. 2). This may be compared to a forest fire spreading by

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engulfing the adjacent areas. The final outcome of an ischaemic insult and oedema is decided ultimately by the battle between the forces involved in self-propagation of the lesion based on progressive increase in tissue pressure interfering with microcirculation, and the forces engaged in healing and resolution of the ischaemic lesion. The latter are related to the most vigorous intracellular uptake of cellular debris and of extravasated proteins by predominantly macrophagic cells, and by formation of a dense mesodermal and glial scar tissue.

There is increasing evidence that the ischaemically injured neurones have a considerable capacity for recovery. This assumption accords with observations of Symon (1985) indicating different CBF thresholds for EEG changes, onset of oedema, interference with ionic pumps and irreversible neuronal destruction. It is therefore possible that most of the regions of penumbra can recover fully, and this should provide a stimulus to concentrated research on factors which may influence recovery after ischaemia. Unquestionably, the mechanisms related to development and dynamics of ischaemic oedema should be the main focus of attention.

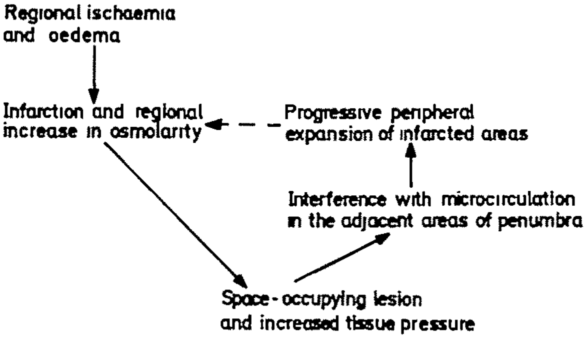
Regional ischaemia and oedema
Infarction and regional increase in osmolarity
Progressive peripheral expansion of infarcted areas
Interference with microcirculation in the adjacent areas of penumbra
Space-occupying lesion and increased tissue pressure

FIG 2 Diagram indicating a sequence of events in the progressive development of ischaemic lesions.

Therapeutic considerations

The recognition of the major mechanisms involved in various phases of IBO provides guidance in the search for rational therapeutic measures.

With regard to CBO, attempts may be made to influence the primary injury responsible for induction of cytotoxic swelling. In this respect, it was shown that early application of hypothermia, phenobarbitone or other metabolism-reducing agents, may dramatically reduce the intensity of ischaemic injury and associated oedema. Otherwise, the application of hyperosmotic therapy, using mannitol, glycerol, etc., appears to be indicated primarily in CBO, since in the vasogenic type of oedema in areas with increased BBB permeability, the influx of hyperosmotic fluid may further increase water content. Nevertheless, in critical situations, prompt application of osmotically active agents or surgical decompression may be required to break a "vicious circle" which may become established when a further increase in intracranial pressure leads to impairment of the microcirculation, which in turn increases ischaemic oedema and further increases intracranial pressure.

With regard to VBO, the "tightening" of the BBB to prevent leakage of serum proteins would be important. So far, the search for agents inhibiting opening of the barrier has not been very successful. The mode of action of steroids still remains obscure, although dexamethasone has proved to be most effective in vasogenic oedema associated with brain tumours and abscesses. According to assumptions in the studies of Reulen and colleagues (1976), reduction of CSF pressure may increase clearance of oedema fluid into ventricles, and this may also be accomplished by curtailing CSF production with some diuretic drugs, such as furosemide and acetazolamide. Effective application of these drugs in combination with dexamethasone in cold injury oedema was demonstrated by Long, Maxwell and Choi (1976).

In recent years, there have been suggestions that, in various forms of brain injury, release of certain compounds from the damaged tissue may be responsible for increase in cerebrovascular permeability, thereby promoting the development of oedema. Thus fatty acids, especially arachidonic acid, or peptides, such as kinins, have been implicated as possible oedema activators (Baethmann 1978). Also, some studies have suggested that the release of serotonin, which was reported to increase cerebrovascular permeability (Westergaard, 1980) and prostaglandins, synthesized in the area of lesion, may affect the dynamics of oedema. It can be assumed that the synthesis of appropriate inhibitors will probably result in agents with some beneficial effects in the treatment of oedema.

In general, treatment of IBO should be flexible, adjusted to the predominant pathological mechanism in a particular phase of oedema and it should be directed also to regulation of various extracerebral parameters. Thus, control of systemic arterial pressure within normal limits is of great importance, since increased arterial pressure was shown to accelerate greatly the spreading of VBO (Klatzo et al., 1967), and to increase an ischaemic injury (Ito et al., 1978). In contrast, reduction in arterial pressure may intensify interference with CBF in the ischaemic regions. Based on meticulous control and adjustment of various extracerebral parameters, Hossmann (1984) recently reported a successful restitution of various brain functions in cats subjected to 1 h of complete, global ischaemia. Such observations should provide a further stimulus in our search for measures which may effectively ameliorate or prevent brain damage induced by cerebral ischaemia.

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Br. J. Anaesth. (1985), 57, 23–33

IONIC CHANGES IN BRAIN ISCHAEMIA AND ALTERATIONS PRODUCED BY DRUGS

D. HEUSER AND H. GUGGENBERGER

The ionic composition of the extracellular fluid surrounding all cells of the central nervous system is maintained under constant physiological conditions. This homeostasis involves the existence of ionic gradients across cell membranes which are maintained by energy-dependent pump mechanisms requiring normal oxygen and substrate supply. Within certain limitations, changes in the ionic balance of cerebral extracellular fluid may, therefore, indirectly reflect the state of cellular energy balance. Dynamic changes in the cerebral extracellular ionic microenvironment became amenable to analysis with the advent of microelectrode techniques adapted specifically for brain extracellular fluid. Such an electrode system may be designed as a single-barrelled, double-barrelled or even multi-barrelled system, depending on the experimental conditions involved. The sensitive site usually consists of glass capillaries with tip diameters of 0.5–5 μm, and a silicone coating on the inner surface. The tip is filled with a liquid ion exchanger which is specifically selective for the ion under investigation, for example K^+, Ca^{2+}, Cl^-, H^+. The exchanger column is covered with an internal filling solution of

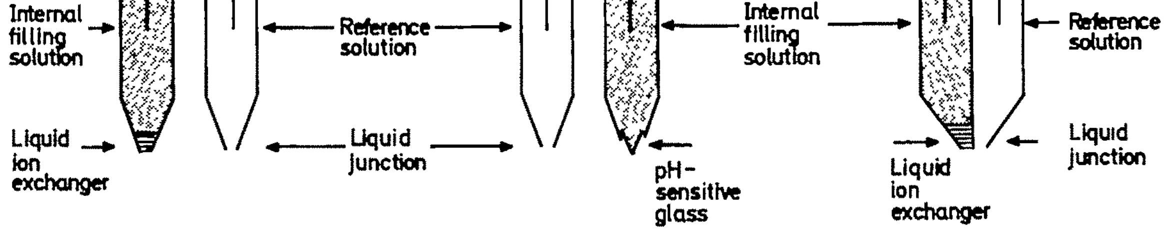

FIG 1. Schematic diagram of single-barrelled and double barrelled microelectrode systems. The diameters of the tip are between 0.5 and 5 µm. The liquid ion exchanger used in the present experimental study was kindly provided by Prof. W. Simon, ETH Zurich, Switzerland, which we gratefully acknowledge.

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constant ionic composition containing a standardized activity of the ion of interest and the generated potential is measured against a suitable reference situated as close as possible in the same medium (fig. 1). For pH measurements, the sensitive tip is made usually of pH-sensitive glass which is melted with a microforge onto an insulating shank of normal capillary tubing. All these electrodes are highly selective and usually exhibit a nearly ideal Nernst response—that is between 50 and 60 mV per 10-fold change in activity measured across the differential input of operational amplifiers with high input impedence.

These electrodes have been used for continuous measurement of local activity changes of several ion species in brain ECF under various physiological and pathophysiological conditions, including activation and depression of central nervous structures, in addition to hypoxia and disturbances in glucose metabolism (Vyskocil, Kriz and Bures, 1972; Astrup and Norberg, 1976; Heuser et al., 1977; Astrup et al., 1978; Heuser, 1978; Nicholson, 1980). In the following review, however, the emphasis is placed on ionic variations in cerebral ischaemia, and new data are presented on possibilities for pharmacologically induced modifications.

IONIC CHANGES IN CEREBRAL ISCHAEMIA

Critical decrease in cerebral perfusion is a serious complication of various intraoperative conditions, not only concomitant with surgical interventions (e.g. sudden blood loss, rupture of brain nutrient vessels during vascular surgery), but also in anaesthetic management (e.g. during pharmacologically induced cardiac arrest, severe controlled hypotension or prolonged extracorporal circulation). In the context of one classification of cerebral oxygen deficiency, it is possible to discriminate between complete cerebral ischaemia and incomplete cerebral ischaemia, each of which may be subgrouped into global and focal circulatory impairment. Hypoxic hypoxia and hypoglycaemia have been described elsewhere (Astrup et al., 1978) and are not discussed in this review.

Complete ischaemic hypoxia

In addition to loss of consciousness within 6–7 s and abolition of EEG activity within 10–20 s (Rossen, Kabat and Anderson, 1943), cessation of cerebral circulation is also accompanied by immediate depletion of cellular energy stores which in turn results in ion pump inhibition, breakdown of ionic gradients across cell membranes, and concomitant membrane depolarization (Ljunggren, Schutz and Siesjö, 1974; Hossmann, Sakaki and Zimmermann, 1977; Astrup, Rehncrona and Siesjö, 1980; Heuser, Morris and McDowall, 1981). Thus, changes in electrolyte distribution occur, including increase in extracellular potassium and decrease in extracellular calcium, sodium and chloride concentrations (Hansen, 1981). Ischaemic brain swelling and shrinkage of extracellular space occur as a result of water and electrolyte shifts. Concomitant with functional membrane failure, there is activation of intracellular processes and this leads to irreversible structural damage (Siesjö, 1981).

Potassium. It is well known that K^+ distribution across cell membranes is directly dependent on the Na^+–K^+ pump which re-establishes the normal transmembrane gradient after transient changes occurring during activation. As a result of ischaemic energy deficiency, K^+ leaks out of the cell in three steps (fig. 2):

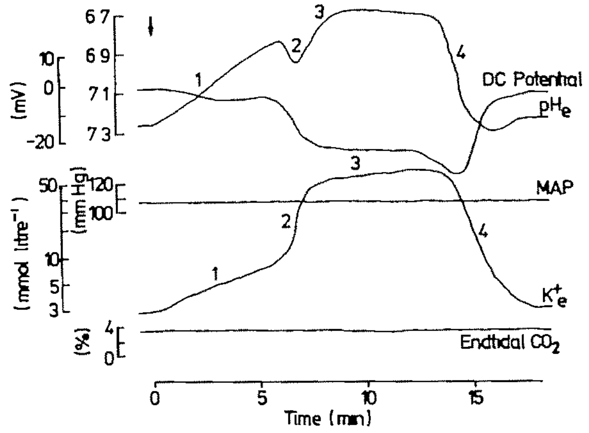

FIG 2. Extracellular pH, K^+ activity and DC potential during complete cerebral ischaemia induced by clipping the middle cerebral artery. The ion-selective electrodes are situated in the ischaemic core. One can clearly identify three phases (1–3) of ionic variation during cerebral ischaemia, followed by the reperfusion period (4). Mean arterial pressure (MAP) and the capnogram were not affected

(1) A slow continuous increase in the extracellular K^+ activity up to 9–10 mmol litre^{-1}, commencing from several seconds to approximately 1 min after the onset of ischaemia.

(2) A second phase of cellular K^+ release characterized by sudden rapid increase in K^+_e to 50–60 mmol litre^{-1} (i.e. anoxic depolarization).

(3) A third phase which is again slower and involves the approach of ceiling values at approximately 65–75 mmol litre^{-1}.
(4) During reperfusion, normal K^{+}concentrations may be re-established quickly, depending on the quality of post-ischaemic flow recovery. Non-pharmacological modification of the time course of these changes, that is the provision of a certain amount of membrane stability, is provided by hypothermia and high glucose availability (Artru and Michenfelder, 1981; Astrup et al., 1981; Heuser et al., 1984; Siemkowicz and Hansen, 1981). K^{+} release is delayed under both conditions; during hyperglycemia, however, K^{+} release is delayed at the expense of enhanced tissue acidosis.

Sodium. Extracellular Na^{+} activity is lower in brain (135 mmol litre^{-1}) than in blood (150 mmol litre^{-1}). During ischaemia the activity of this cation varies in a manner opposite to changes in extracellular K^{+} (Hossmann, Sakaki and Zimmermann, 1977). However, cellular Na^{+} uptake considerably exceeds intracellular cation content and this is consistent with von Harreveld's hypothesis of active Na^{+} transport into the cell, accompanied by water uptake to maintain osmotic equilibrium (Van Harreveld and Ochs, 1956; Van Harreveld, 1966). As with K^{+}, Na^{+} homeostasis can be re-established during adequate recirculation.

pH. During complete interruption of cerebral circulation, extracellular pH (pH$_e$) decreases rapidly, attaining values between 6.7 and 6.2 (fig. 2). This decrease in pH$_e$ occurs usually in three steps: an initial decrease (1) is followed by a brief increase at the time of anoxic depolarization (2), which is followed by a further slow shift in the acidic direction (3). As may be seen from metabolic data, this decrease in pH$_e$ approximates the time course of the increase in brain lactate, in addition to decrease in brain glucose and energy-rich phosphates (Siesjö, 1978). Some minutes after anoxic depolarization (termination of anaerobic glycolysis), the increase in H$^{+}_{e}$ ceases. However, the stage of rapid worsening of ECF acidosis directly after anoxic depolarization may partly result from Na^{+} entering the cells and displacing intracellular H^{+} ions, but other mechanisms could be involved also (Mutch and Hansen, 1984; Siesjö, 1984). During reperfusion, extracellular pH occasionally declines further before moving towards renormalization, which is attained approximately 6–30 min later.

The time course and the degree of pH$_e$ variations during ischaemia can be modified by inhibitors of carbonic anhydrase, Na^{+}/H^{+} countertransport (amiloride) and Cl^{-}/HCO$_3^{-}$ countertransport (4,4 diisothiocyanostilbene-2,2′ disulphonic acid) which suggests new possibilities for brain pH regulation (Mutch and Hansen, 1984). However, intracellular and extracellular pH are dissociated, as indicated by early intracellular alkalosis in the recovery period (Siesjö, 1984). Hypothermia and hypoglycaemia delay development of acidosis which, conversely, may be enhanced by pre-ischaemic glucose loading (Heuser et al., 1984). This is of particular significance with regard to structural damage, since severe lactic acidosis has been suggested as one of the most important factors facilitating irreversibility of tissue damage during ischaemia (Kalimo et al., 1981).

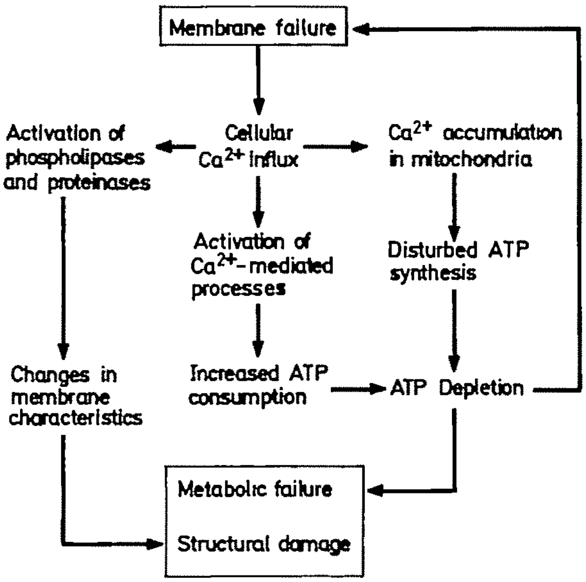
Membrane failure
Activation of phospholipases and proteinases
Cellular Ca2+ influx
Ca2+ accumulation in mitochondria
Activation of Ca2+-mediated processes
Disturbed ATP synthesis
Changes in membrane characteristics
Increased ATP consumption
ATP Depletion
Metabolic failure
Structural damage

FIG 3. Ca^{2+}-mediated processes which may lead to cellular metabolic failure and structural damage after ischaemic membrane failure has occurred.

Calcium. Under physiological conditions, a 10 000:1 concentration gradient of Ca^{2+} across the cell membrane (Katz and Reuter, 1979) is maintained by at least two ATP-dependent pump mechanisms: a unidirectional Mg^{+}-dependent pump and a calcium–sodium exchange mechanism which moves calcium out of the cell (Dipopolo, 1978). The specific role of this ion has been extensively investigated during the past 10 years in a wide variety of pathophysiological conditions in different organs. Thus, changes in Ca^{2+} have been linked to modifications of cellular metabolism, production of oxidative free radicals, release of free fatty acids, and flow alterations in the post-ischaemic period. Since all these events are involved in the mechanisms of ischaemic cell death, analysis of Ca^{2+} homeostasis during ischaemia and attempts to prevent its derangement by pharmacological means seem promising with regard to brain protection. Various investigators have shown that the decrease in the transmembrane potential during ischaemia opens voltage-dependent Ca^{2+} gates and the decrease in the transmembrane Na^+ gradient slows outward transport of calcium. The resulting Ca^{2+} influx in addition to release of Ca^{2+} from mitochondria and endoplasmic reticulum leads to a dramatic Ca^{2+} increase in the cytosol (fig. 3). This process initiates harmful reactions, for example activation of phospholipase A_2 with liberation of free fatty acids including arachidonic acid in particular (Siesjö, 1978).

If ischaemia ceases—even after 20–30 min—and adequate reperfusion is established, the transmembrane Ca^{2+} gradient is restored quickly and normal Ca^{2+}_e is attained usually before normalization of K^+_e and pH.

Incomplete ischaemic hypoxia

If cerebral ischaemia is not complete, the typical changes in ionic equilibrium do not occur precisely as described above, and they depend on the residual levels of flow in addition to the remaining cerebral availabilities of oxygen and glucose. Nevertheless, the pathophysiology of the syndrome of incomplete cerebral ischaemic hypoxia is of major significance to the anaesthetist, since most ischaemic insults are incomplete, and total circulatory arrest is the exception—that is, the anaesthetist generally deals with patients undergoing acute stroke, controlled hypotension, shock syndromes of different aetiology and vascular surgery. As noted in previous investigations (Astrup, Symon and Branston, 1977; Harris et al., 1981), analysis of the pathophysiological sequelae has demonstrated clearly that changes in electrical activity and ion homeostasis occur as given thresholds of residual flow (Astrup, Siesjö and Symon, 1981). Thus, electrical activity measured as EEG (fig.4) or evoked somatosensory potentials is abolished at flows of 15–20 ml $min^{-1}/100$ g (Branston, Symon and Crockard, 1974; Heiss, Hayakawa and Waltz, 1976). However, it must be emphasized that this abolition of electrical activity is not linked to membrane depolarization produced by intracellular energy failure and K^+ efflux, since ATP values are still high at this stage although phosphocreatine concentration is already low and lactate

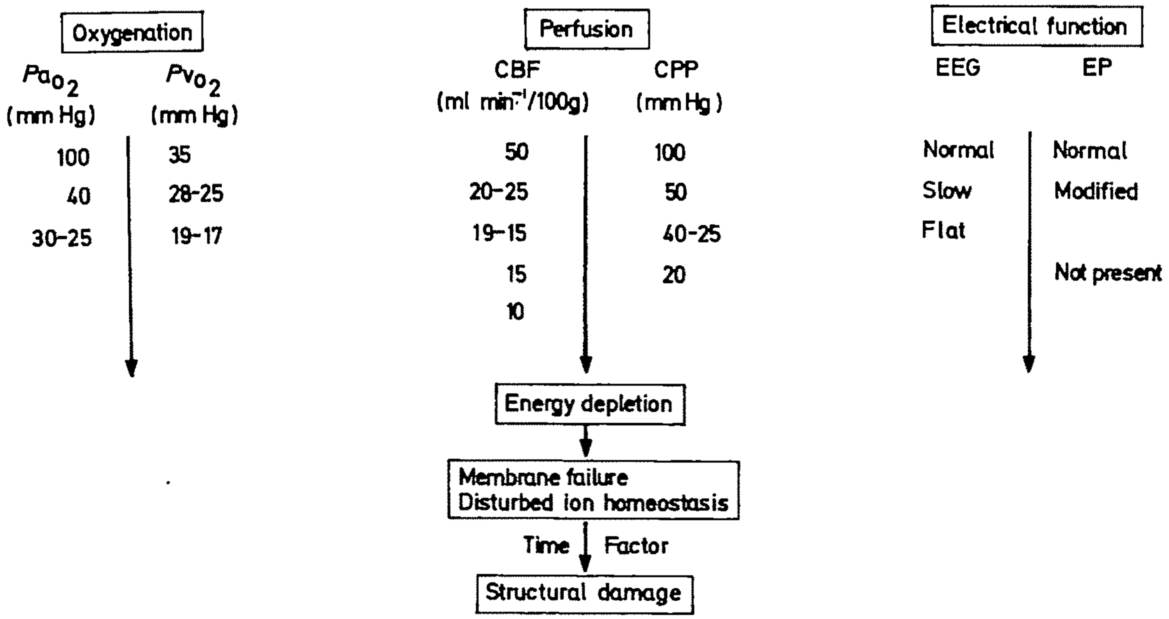

FIG 4. Thresholds of cerebral oxygenation and perfusion causing impairment of electrical function and membrane failure, which is followed, time dependently by cellular structural damage. Electrical function is measured in terms of EEG and evoked potentials.

accumulates in the tissue. Membrane failure occurs when the residual flow approaches values of 10 ml min^{-1}/100 g (Astrup, Symon and Branston, 1977; Heuser, Morris and McDowall, 1981). At this point, ATP depletion occurs, followed by pump failure and ionic imbalance involving K^+, Ca^{2+}, Na^+ and Cl^-. Recent experiments of Harris and colleagues (1981) have indicated that calcium changes have the lowest flow threshold, of the order of 6–9 ml min^{-1}/100 g or approximately 13 mmol litre^{-1} of extracellular K^+. However, such a very close interrelationship between K^+ and Ca^{2+} is not observed regularly, as was evident from the present data with complete and severe incomplete ischaemia (figs 5, 6). As has been noted, the decrease in pH_e during complete cerebral ischaemia stops at values between 6.7 and 6.5. This indicates cessation of glycolysis at the time of anoxic depolarization which, in turn, precedes a further pH_e decrease resulting from enhancement of ECF acidosis, possibly from Na^+/H^+ exchange.

However, if residual flow is present, anaerobic glycolysis continues and therefore generates enormous amounts of lactate, and pH_e values decrease well below pH 6. Since severe lactacidosis is an important factor in structural brain damage, such events are of considerable clinical significance—particularly resulting from accumulation of lactate over time in conditions of only slight circulatory impairment. Thus, a patient with only moderate but long-lasting cerebral circulatory impairment is at much greater risk of developing neurological deficits than a patient with brief circulatory arrest and immediate resuscitation. The significance of lactacidosis for structural tissue damage also emphasizes the necessity of preventing high blood glucose concentrations under the above conditions, since increased glucose availability during critical perfusion conditions may exaggerate tissue acidosis (Heuser et al., 1984).

VASCULAR EFFECTS

The influence of disturbed ion homeostasis on vascular smooth muscle tone is of particular interest, not only in the reperfusion period after ischaemia,

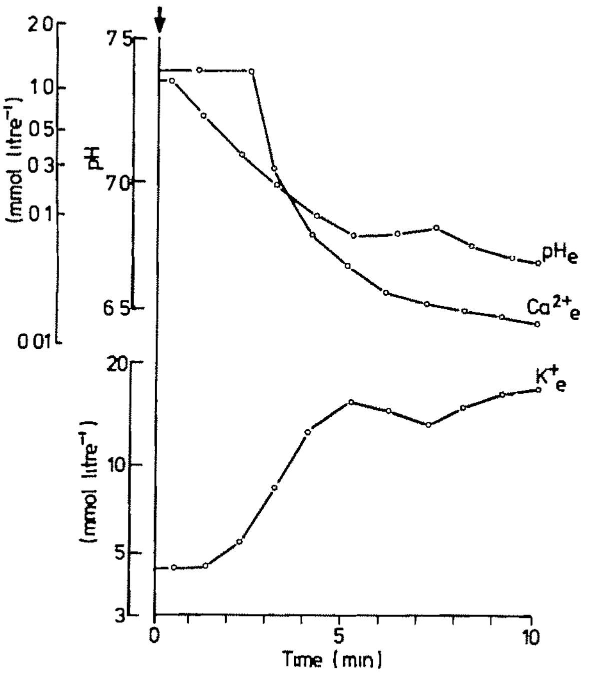

FIG 5. Cerebral extracellular pH, Ca^{2+} and K^+ activities during severe incomplete ischaemia in a cat, produced by a combination of haemorrhagic hypotension and carotid ligation. Extracellular pH decreases immediately at the onset of impaired cerebral circulation, whereas $Ca^{2+}{}_e$ decreases when $K^+{}_e$ is increased to approximately 10–15 mmol litre^{-1}.

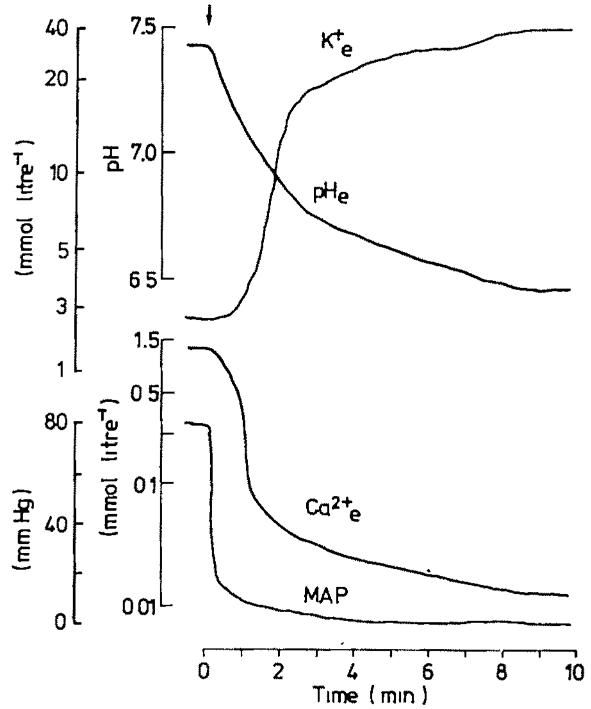

FIG 6. Changes in cerebral ionic homeostasis induced by complete circulatory arrest induced by i.v. injection of KCl in a cat at the end of a single experiment. Start of ionic changes occurs immediately after cardiac arrest and the "typical" time course of ionic changes is not evident.

but also with regard to changes in vascular diameter during the ischaemic event. As has been demonstrated by several groups using the microperfusion technique, changes in the perivascular ionic matrix cause distinct variations in vascular smooth muscle tone (fig.7):

(1) Perivascular acidosis leads to vasodilatation, whereas decrease in H^+ causes vasoconstriction (Betz and Heuser, 1967; Lassen, 1968; Kuschinsky et al., 1972). This access (via variation in $P\mathrm{CO}_2$) to the cerebral vascular smooth musculature is the basis for hyperventilation treatment of patients with increased ICP and for treatment of focal ischaemia, whereby blood from reactive vessels may be "squeezed" into non-reacting vessels in the adjacent ischaemic area.

(2) K^+ has a dual effect on the cerebral vessel wall. Moderate increases up to 10–15 mmol litre^{-1} lead to dilatation, whereas high K^+ concentrations constrict vascular smooth musculature (Betz and Csornai, 1977; Cameron and Caronna, 1976; Kuschinsky and Wahl, 1978; Wade, Amtrop and Sørensen, 1975).

(3) Ca^{2+} increase constricts smooth muscle in addition, whereas Ca^{2+} depletion is followed by distinct vasodilatation (Betz and Csornai, 1978). The effects of these ions on vascular smooth muscle tone interact under physiological conditions, constitute the regulatory mechanism during critical pefusion conditions (fig. 8) and are modified by transmitters and metabolites released under physiological and pathophysiological conditions. '

During incomplete ischaemia, the initially low oxygen availability may be normalized by ion-induced vasodilatation. However, if ischaemia is more severe, the resulting changes in ionic equilibrium—especially high extracellular K^+ and high intracellular Ca^{2+}—aggravate the critical perfusion induced by maximal vasoconstriction, thus initiating a vicious circle which leads to structural damage if critical conditions are maintained (Baldy-Moulinier, 1971; Meyer et al., 1971; Bering, 1974; Wade, Amtrop and Sørensen, 1975).

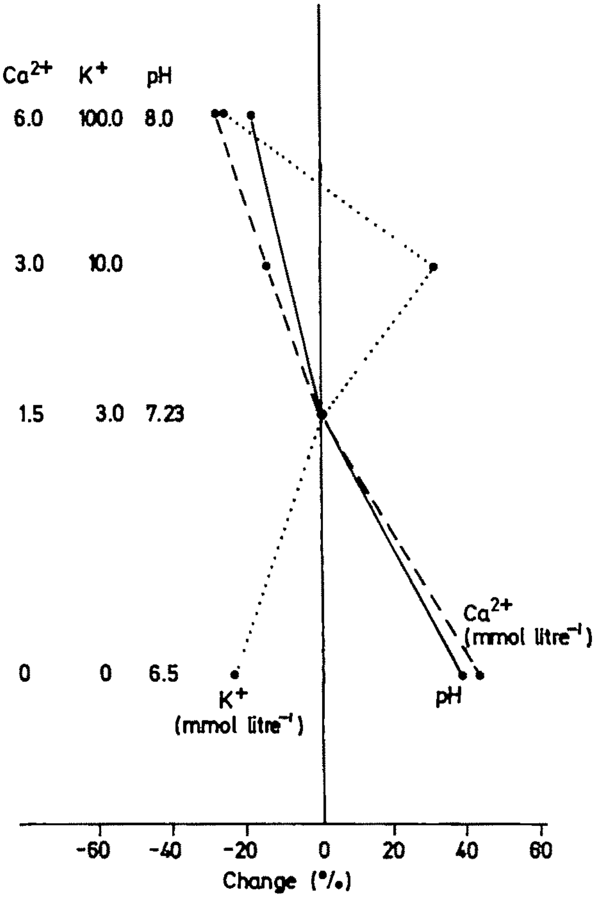

FIG 7. Changes in pial artery diameter (abscissa) induced by changing the perivascular ionic microenvironment using a microperfusion technique. The diagram demonstrates the results of varying only a single ion in the perfusate.

DRUG-INDUCED ALTERATIONS

Although it is not clear what role extracellular cation concentrations play in the functional performance of the whole brain after ischaemic injury, the present considerations and the data available from the literature appear to justify therapeutic attempts to prevent disturbances in cerebral ion homeostasis by the use of pharmacological interventions. Such efforts may block those biochemical reactions which have so far been identified as being most harmful to cellular integrity. In addition to hypothermia, which appears to act protectively by slowing down the cellular metabolic rate, essentially three pharmacological approaches to maintenance of cerebral ion homeostasis in ischaemia have been investigated in recent years:

(1) Membrane stabilization by direct action on the ion transport mechanisms or on the membrane structures.

(2) Metabolic depression to avoid membrane failure, by amelioration of the disturbed relationship between metabolic supply and demand.

(3) Inhibition of calcium-mediated intracellular processes which lead to destruction of cellular struc-

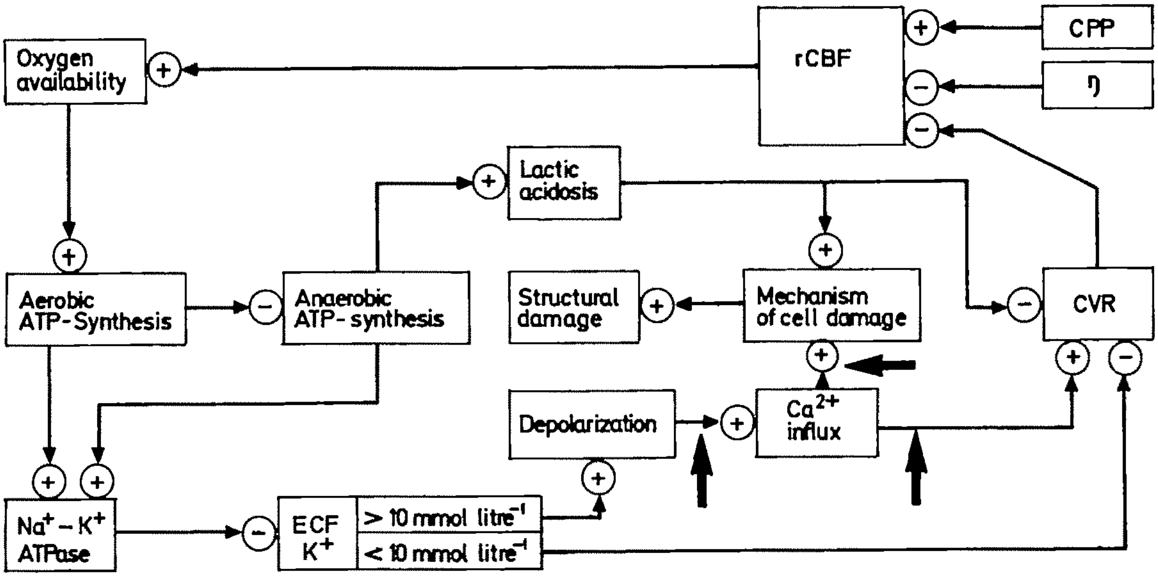

FIG 8. Schematic diagram of ionic control of local cerebrovascular resistance during critical perfusion conditions The large arrows indicate conceivable sites of action of "calcium-entry blockers".

tures by the use of calcium entry-blocking drugs.

Membrane-stabilizing drugs

Lignocaine. As has been known for years, local anaesthetics such as lignocaine block the sodium channels in the cell membrane (Strichartz, 1976). Their influence on ion leakage during ischaemic membrane failure has been investigated by Astrup and colleagues (1981), who have shown that a huge dose of lignocaine 160 mg kg^{-1} significantly delayed the ischaemic K^+ efflux during global ischaemia—an effect which was shown to be additive to that of hypothermia.

Phenytoin. In addition to the barbiturates, phenytoin has been studied extensively in numerous mammalian species under various conditions of reduced cerebral oxygen availability. In almost all studies, a "cerebroprotective effect" was demonstrated in respect of survival time and structural integrity (Cullen et al., 1979). Recent investigations by Artru and Michenfelder (1981) have shown that membrane stabilization (i.e. reduced ischaemic K^+ efflux) is the main effect of the drug which thus may provide cerebroprotection. These results have confirmed indirectly those of Heinemann and Lux (1973) who demonstrated that phenytoin reduced the amplitude of the increase in K^+_e during stimulation of cat cortex. This effect of reduced increase in K^+_e is likely to be explained by:

(1) Reduction of net outward K^+ flux from hypoxic structures (Pincus, Grove and Marino, 1970; Baldy-Moulinier, 1971; Escueta and Appel, 1972).
(2) Enhanced function of the ATP-dependent Na^+/K^+ pump (Festoff and Appel, 1968; Escueta and Appel, 1972; Ferbiger, Liuzzi and Dunham, 1971).
(3) Energy-independent membrane stabilizing effect (Crane and Swanson, 1970; Nasello, Montini and Astrada, 1972; Pincus, 1972).

Metabolic depressant drugs

The study of Bleyaert and colleagues (1978) on monkeys demonstrated that administration of thiopentone produced distinct amelioration of brain damage during global ischaemia. Part of the concept in the use of thiopentone was to reduce cerebral oxygen consumption, and thus prevent mismatch between oxygen supply and demand in critical perfusion conditions. However, a delay in ischaemic K^+ efflux was not detected (Artru and Michenfelder, 1981; Astrup et al., 1981) and Nemoto and Stanley Frinak (1981) demonstrated that post-ischaemic thiopentone loading not only did not accelerate brain pH_e normalization, but actually delayed it, while, in normal brain, pH_e was increased and lactate formation decreased. This delay in normalization of ionic homeostasis has been confirmed by our group with etomidate in a model of severe incomplete ischaemia (fig. 9). In comparison with the controls (fig. 10), normalization of $\mathrm{pH_e}$ and K^+_e was distinctly delayed when the drug was given at the end of the ischaemic period (Heuser and Guggenberger, 1983) (fig. 11). One mechanism of this effect may be the drug-induced inhibition of ATPase activity and thus inhibition of restoration of ionic homeostasis. This inhibition appears to be involved intimately with inhibition of glycolysis. A second explanation may be the impairment of post-ischaemic hyperperfusion, which is regarded as an essential factor in post-ischaemic recovery of ion homeostasis, metabolism and electrical function (Hossmann, Lechtape-Grüter and Hossmann, 1973). When the drug was administered in the pre-ischaemic period, however, K^+_e was significantly lower at the end of ischaemia while the degree of extracellular acidosis was not affected. However, normalization of ion homeostasis in this group occurred faster than in the control group, and this may indicate better preservation of intracellular ATP stores during the experimental conditions of severe incomplete ischaemia. We are sure that such improved preservation of ATP stores is of considerable significance in clinical situations in which severe incomplete ischaemia is likely to occur, for example sudden blood loss, deep controlled hypotension, prolonged extracorporal circulation. The clinical implications are that administration of short-acting metabolic depressant drugs might be beneficial before critical events or throughout anaesthesia using anaesthetics (such as isoflurane) which provide distinct depression of metabolism while increasing flow conditions (Newberg and Michenfelder, 1983).

Calcium-entry blockers

As mentioned above, Ca^{2+} accumulation in the cytosol following membrane depolarization and Ca^{2+} influx, is an event of great importance in the pathophysiological sequelae of cerebral ischaemia (Schanne et al., 1979; Farber, Chien and Mittnacht, 1981; Hass, 1981; Symon, Harris and Branston, 1982; Wieloch, Harris and Siesjö, 1982). This also applies particularly to vascular smooth muscle cells, in which the Ca^{2+}-induced vasoconstriction may enhance the critical reduction in oxygen supply which has already occurred (Betz and Csornai, 1978). In order to prevent or at least modify these deleterious reactions, "calcium-entry blockers" have been investigated *in vitro* and *in vivo* with the aim of improving the pathophysiological conditions of man and animals suffering from different degrees of cerebral ischaemia (Edvinsson et al., 1979; Hoffmeister, Kazda and Krause, 1979; Harris et al., 1981, 1982; White, Gadzinski and Hoehner, 1982; Steen et al., 1983). In contrast to results in man and animals indicating inhibition of vasoconstrictor stimuli following subarachnoid haemorrhage (Auer et al., 1982; Auer, 1983) or post-ischaemic hyper-

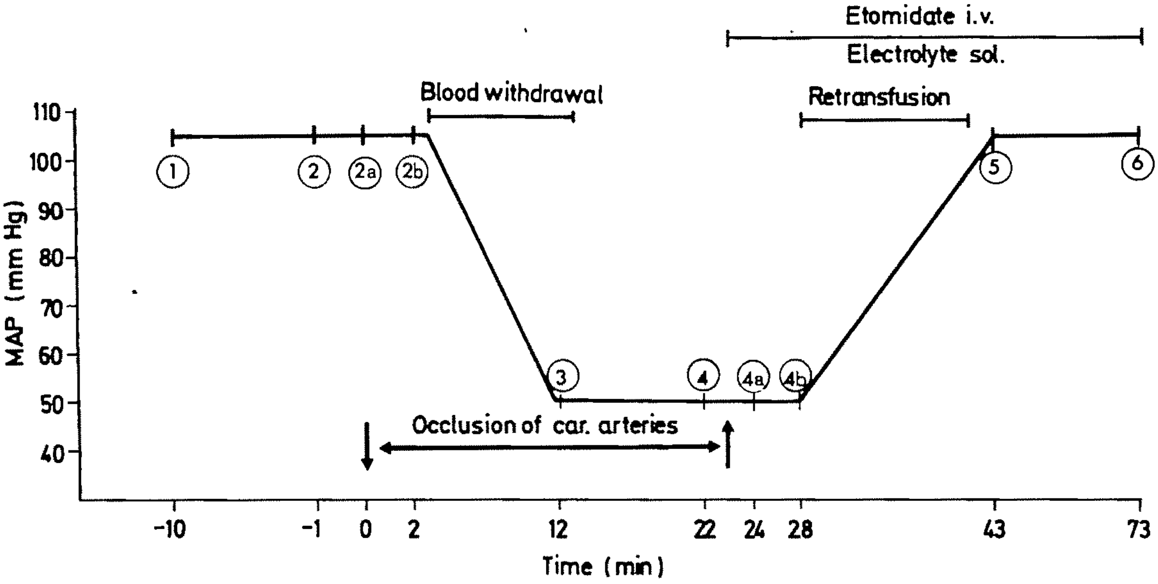

FIG 9. Experimental design of our model of severe incomplete cerebral ischaemia in cats, produced by a combination of carotid ligation and haemorrhagic hypotension. At certain intervals (numbers in circles) the following variables were measured: CBF, BGA, haemoglobin, PCV, glucose, EEG.

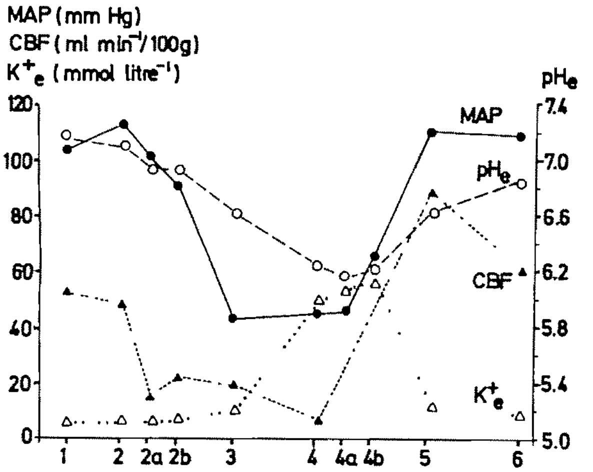

FIG 10. Extracellular pH and K^+, local cerebral blood flow (CBF, H_2 inhalation clearance) and mean arterial pressure (MAP) during severe incomplete ischaemia and recovery in cats (see also fig. 9).

perfusion, direct evidence for stabilized extracellular Ca^{2+} in the course of ischaemia has not yet been forthcoming. Symon, Harris and Branston (1982) failed to demonstrate an effect on the decrease in extracellular Ca^{2+} during ischaemia induced by clipping the middle cerebral artery. Furthermore, they emphasized the possible deterioration of the intracranial situation, when the drug is administered in conditions with already reduced intracranial compliance. Under such conditions, a further increase in cerebral intravascular volume may decrease cerebral perfusion pressure via increased intracranial pressure. Studies with the Ca^{2+} entry blocker flunarizine are currently in progress in our laboratory and seem to be promising with regard to prevention of ischaemic Ca^{2+} fluxes. Indirect evidence of Ca^{2+} accumulation in the cytosol under the influence of these drugs has already been reported by Shiu and colleagues (1983), who demonstrated reduced liberation of free fatty acids. However, such an effect could also have been induced by diminished release of Ca^{2+} from intracellular stores. The influence of these drugs on cerebral homeostasis of other ions is worthy of further investigation.

CONCLUSIONS

The significance of cerebral ion homeostasis in cellular integrity during ischaemia has become evident, based on the wealth of data presented in the past 15 years. However, the possibilities of therapeutic intervention in disturbed ion homeostasis are fairly limited and provide only minutes of delay before the onset of critical reactions. It seems evident, therefore, that the attention of the clinician should be directed primarily to two areas:

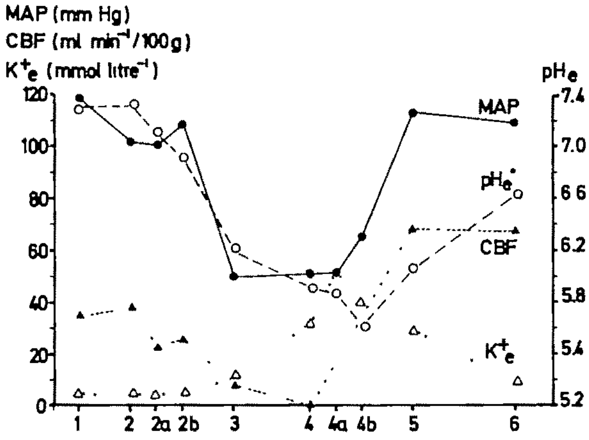

FIG 11. Extracellular pH and K^+, local cerebral blood flow (CBF) and MAP during severe incomplete ischaemia and recovery in cats (mean of 10 animals). Etomidate (5 mg kg^{-1} initially, followed by 4 mg kg^{-1} h^{-1}) was administered at the end of the ischaemic period. Post-ischaemic hyperperfusion is impaired, as is normalization time of disturbed ion homeostasis.

(1) The potential consequences of critical cerebral perfusion conditions, for example during drug-induced hypotension (Morris et al., 1983) and especially in long-term conditions with only slightly impaired circulation since the imminent hazards of such situations are not obvious to the anaesthetist.

(2) Drug administration during incomplete cerebral ischaemia. Drugs may be administered in the early phase of circulatory impairment and should include metabolic depressant drugs, phenytoin or calcium antagonists. Among the inhalation agents, isoflurane seems to be the anaesthetic which most appropriately fits the present concept. However, the specific limitations of such therapy should be carefully considered in the light of the patient's pathophysiological condition.

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FLOW THRESHOLDS IN BRAIN ISCHAEMIA AND THE EFFECTS OF DRUGS

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The concept of ischaemic thresholds arose from clinical observations; in clinical neurosurgery, for example, patients recovering from anaesthesia may show progressive clearance of a neurological deficit, while some patients who develop a deficit with low arterial pressure clear that deficit promptly when the arterial pressure is increased. Patients with established cerebrovascular occlusion and dense neurological deficit show evident improvement over months or years, and while some potential for relearned circuitry in the nervous system may play a part, it seems likely that, in many acute circumstances, neurones which at one time were apparently non-functional, may return to normal function under improved conditions of perfusion.

The electrical function of the central nervous system has been assessed from a variety of standpoints. Studies have been undertaken of the differential effects of ischaemia on the electrophysiological activity of presynaptic terminals and synaptic transmission (Collewijn and Van Harreveld 1966a, b), of the concomitants of ischaemia such as changes in tissue impedance, surface potentials, transmembrane ionic and water shifts, and histological damage (Van Harreveld and Tachibana, 1962; Collewijn and Van Harreveld, 1966a, b; Hossmann, 1971; Brierley et al., 1973) and of correlation between cerebral blood flow, intracranial pressure and the direct cortical response (Grossman et al., 1973). Clinical studies have related regional cerebral blood flow and EEG (Ingvar, 1970; Boysen, Engell and Trojaborg, 1973), while the well-established sequence of changes in the EEG caused by various forms of anoxia has been reviewed (Meyer and Marx, 1972). There is also developing interest in the survival of neuronal function following ischaemia (Hossmann and Sato, 1971; Przybylski, 1971). However, in most of the experimental studies the ischaemia produced has been total and widespread. This is at variance with the clinical situation, where complete ischaemia is most unusual, for example in cerebrovascular disease. It would be of great interest to analyse the effects of partial ischaemia upon cerebral function experimentally and to establish quantitative changes in electrical activity corresponding to different degrees of cerebral ischaemia.

An electrical threshold in acute brain ischaemia

Occlusion of the middle cerebral artery in an experimental primate simulates an acute clinical stroke (Harvey and Rasmussen, 1951; Symon, 1961; Yamaguchi, Waltz and Okazaki, 1971; Symon, Dorsch and Ganz, 1971). The extent of the ischaemic lesion is restricted to known regions of the cerebral hemisphere and interferes only selectively with neural pathways. It has been shown (Symon, Pasztor and Branston, 1974) that the density of the ischaemia produced by occlusion of the middle cerebral artery is graded over the surface of the hemisphere, so that different levels of residual flow result at different positions on the hemisphere. In particular, such a gradient is present along the sensorimotor strip. Since the thalamic nuclei are not affected significantly by occlusion of the middle cerebral artery (Lazorthes and Campan, 1964; Kaplan and Ford, 1966), changes in somatosensory evoked potential from peripheral stimulation (Prior, 1985) observed after occlusion can be related directly to changes in tissue flow in the region of the recording electrode. Measuring flow by the highly focal technique of hydrogen clearance (Pasztor et al., 1973) in the immediate area of the evoked potential electrode, we have been able to relate electrical activity to flow at selected positions on the cortex.

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These experimental observations indicated that the primary positive/negative wave of the somatosensory evoked response (SEP) was fully maintained down to blood flows of approximately 20 ml min^{-1}/100 g from a control value of 50 ml min^{-1}/100 g. At this point there was a sharp decline in evoked response, with complete disappearance by 12 ml min^{-1}/100 g. The half value for the "threshold" was 16 ml min^{-1}/100 g.

In a separate species, using intracellular microelectrode recording, Heiss, Hayakawa and Waltz (1976) suggested a threshold value of 18 ml min^{-1}/100 g for spontaneous neuronal activity in the cat. These experimental and carefully controlled observations accorded well with clinical observations (Trojaborg and Boysen, 1973) in carotid disobliteration operations, suggesting that the EEG was critically impaired at values of CBF less than 20 ml min^{-1}/100 g. In all our subsequent experimental work, this approximate value of 15–20 ml min^{-1}/100 g for an electrical threshold has been sustained. Because of the ease of interpretation of evoked potential records, such work may be transferred directly to the clinic.

In a recent series of experiments, SEP and CBF in thalamus and brain-stem (medial lemniscus) have been measured and the effects of induced ischaemia assessed. Middle cerebral occlusion abolished the early components of the response in cortex on the affected side, while the ventrolateral thalamus and medial lemniscal responses were unaffected. Thereafter, progressive hypotension was used serially to reduce and finally to abolish the thalamic response, the medial lemniscus proving most resistant to ischaemia. In lemniscus, the response was sustained down to at least 10 ml min^{-1}/100 g, in contrast to the situation in cerebral cortex. With the corresponding ventro-posterior laminar nucleus (VPL) plot, the contrast with cortex was not so great as with that of the medial lemniscus, but there were several data points well above the zero level in the region of 10 ml min^{-1}/100 g. The situation was clearer in relation to hypotension, the lemniscal volley being preserved down to arterial pressures of 20–30 mm Hg. Comparing the data of CBF and mean systemic arterial pressure in bands of equal width, we found that in the flow band 15–20 ml min^{-1}/100 g, cortical SEP was reduced significantly, whilst VPL and lemniscus were not significantly different from control. In the range 10–15 ml min^{-1}/100 g, VPL was reduced significantly, and cortical response almost abolished. The lemniscal response was reduced similarly only below a flow of 10 ml min^{-1}/100 g.

Thus, as one descends the neuraxis there is an increasing resistance of electrophysiological function to ischaemia. It has been noted (Gregory et al., 1979) that failure of the cortical SEP may arise from reduction in CBF in subcortical segments of the afferent pathway in addition to cortex. Our present results show that (at least up to the level of the thalamus) the possibility of prior subcortical transmission failure is unlikely in progressive hypotension, since VPL and lemniscus are less sensitive to ischaemia than cortex.

Ionic thresholds

Electrical function is related closely to rCBF, and the complete electrical failure below the ischaemic threshold might result from synaptic depolarization (Branston et al., 1974) subsequent to release of cellular potassium into the extracellular space (Marshall et al., 1975). Other conditions, however, are also known to accompany ischaemia; change in neurotransmitter metabolism or tissue lactacidosis have been discussed in relation to complete electrical failure (Marshall et al., 1975).

In a further study, therefore, we tested the association between electrical function and extracellular activities of K^+ and H^+ (K_e and pH_e) at the ischaemic threshold of electrical failure (Astrup et al., 1977). Using a preparation similar to that already described, we found a mean extracellular potassium concentration (maintained steady for at least 30 min before the clip) of 5.5 mmol (SD 1.3). Corresponding tissue flows were in the normal range (mean 105 ml min^{-1}/100 g, SD 24) (Pasztor et al., 1973). The extracellular potassium concentration in the cortex remained normal or only slightly increased at the threshold when electrical function ceased (Astrup et al., 1977).

Increase in extracellular potassium concentration, indicative of "pump failure", did not occur unless local blood flow was reduced further. In these (Astrup et al., 1977) and in subsequent studies on the baboon with middle cerebral artery occlusion, it was possible to determine a critical ischaemic flow threshold of approximately 10 ml min^{-}/100 g, below which the extracellular potassium concentration increased massively by efflux of potassium from the cells. Further studies in the rat with bicuculline-induced continuous generalized seizures have confirmed this observation (Astrup, Blennow and Nilsson, 1979).

At the point of seizure interruption, the extracellular potassium concentration decreased, indicating that sufficient energy remained for ion pumping. This was verified by direct tissue analyses, in which, although lactic acid concentrations were increased and phosphocreatine decreased, the ATP concentration was close to normal.

The vital role of calcium in normal cellular function has been the subject of many investigations, and in recent years the pathological effects of intracellular calcium accumulation have become apparent (Zimmerman and Hulsman, 1966; Shen and Jennings, 1972). The myocardial changes associated with reperfusion have been reviewed by Hearse (1977), and it has been suggested that the mechanisms of damage associated with calcium uptake are, first, that the ability of the intracellular membranes to withstand or control sudden ion fluxes is reduced, and second, that the physical effects of calcium uptake and deposition destroy mitochondrial function. In the light of such work on calcium homeostasis in myocardium and elsewhere, it seemed to us that a fuller understanding of the calcium changes in the cerebral cortex in ischaemia and on reperfusion might be of critical value in determining the survival of cerebral tissue.

Changes in the activity of calcium in the extracellular space of brain are known to occur. Nicholson's group has shown relationships between extracellular potassium activity (K_e) and calcium activity (Ca_e) in spreading depression and terminal anoxia in cerebral cortex and cerebellum (Kraig and Nicholson, 1978; Nicholson, 1980).We have measured Ca_e and related the changes in partial ischaemia of the primate cerebral cortex to K_e and local cerebral blood flow (lCBF). Analysing the association of ion changes by the use of triple-barrelled, double-ion sensitive microelectrodes we have measured both K_e and Ca_e in the same extracellular site simultaneously.

K_e and Ca_e were measured at 12 sites in six animals. The respective base-line values measured during the control period were K_e 3.95 ± 0.8 mmol and Ca_e 1.31 ± 0.01 mmol (mean ± SD). The values for K_e and Ca_e were taken from each electrode at each lCBF determination so that activity–flow relationships could be determined. At a blood flow of approximately 10 ml $\text{min}^{-1}/100$ g there was a threshold below which there was a major change in extracellular ion activities. Although the threshold blood flows for potassium and calcium change could not be distinguished statistically, it can be shown in other ways that the events were not simultaneous. The triple-barrelled electrode can show accurately the relationship between K_e and Ca_e at the same point.

Spontaneous transient changes in K_e and Ca_e were seen also and these events shed further light upon the relationship between K_e and Ca_e. In spontaneous transient changes, as in ischaemia, K_e began to increase before Ca_e decreased, with an average delay of 13.7 ± 3.7 s. The K_e value attained before Ca_e moved was 10.5 ± 3.0 mmol, which is not significantly different from the K_e value associated with Ca_e movement in ischaemia.

The relationship of calcium changes in ischaemia to K_e has been substantiated by the demonstration that, although the value of K_e associated with the decrease in Ca_e is always the same, the delay between potassium and calcium changes is related to blood flow. The increase of extracellular potassium in ischaemia undoubtedly results from progressive overload of potassium clearance mechanisms with increased leakage of intracellular potassium (Astrup et al., 1977; Branston, Strong and Symon, 1977; Hossmann, Sakuki and Zimmerman, 1977). It might be expected that the time taken to reach the threshold K_e value of 13 mmol would thus be dependent upon blood flow. The increased leakage of intracellular potassium before any change in Ca_e indicates that there is a differential sensitivity of ion homeostatic mechanisms to ischaemic damage.

The relationships between K_1, K_2 and Ca_1 suggest that availability of cellular energy may provide an alternative to depolarization as the explanation for calcium movement. K_2 is greater than K_1 in every instance and it may be that the point at which the rate of potassium efflux increases (which is also the point at which Ca_e begins to decline exponentially) is the time when the reduced cellular energy can no longer maintain ion homeostasis. The relationships between K_1 and both K_2 and Ca_1 serve to strengthen this hypothesis. The relationship between K_2 and Ca_1 suggests that the cell membrane becomes more permeable to both ions in the same proportion.

The increase in extracellular potassium activity in ischaemia and decrease in subarachnoid sodium activity as described by Hossmann, Sakuki and Zimmerman (1977) have been interpreted as a redistribution of ions down their concentration gradients across the membranes of cellular elements. In view of the large decrease in extracellular calcium activity, it seems reasonable to suggest that the same explanation applies to the calcium change. This proposal for movement of calcium into the cells is corroborated to some extent by calculation of the Ca_e that would be present if all calcium activity were redistributed evenly between intra- and extracellular compartments in ischaemia. If we allow for the changes in compartment size as reported by Hossmann, Sakuki and Zimmerman (1977) and presume that there is no net change in calcium activity, the value attained by Ca_e should be 0.25 mmol. The final Ca_e found in densely ischaemic tissue (lCBF 6 ml min^{-1}/100 g) in this preparation was 0.28 mmol, indicating that the calcium activity in the intra- and extracellular compartments were in equilibrium. The proposal of intracellular movement is substantiated further by the work of Adey (1971), who showed that although membrane complexing of calcium does occur, this effect is probably modest.

The relationship between K_e and Ca_e indicates that as K_e increases to the threshold value of 13 mmol, there is a slight increase in Ca_e. The explanation for this may lie in either a change in the binding coefficient for calcium in the extracellular space, or, more probably, a decrease in the size of the extracellular space (ECS) without any loss in calcium. This would be measured as an increase in Ca_e. Rapid changes in the ECS in ischaemia have been demonstrated from impedance measurements (Branston, Strong and Symon, 1978), and the use of choline and Tris as an *in vivo* marker of the ECS (Hansen and Olsen, 1981).

Hass (1981) has suggested recently a hypothesis for the molecular mechanism of cellular damage resulting from increased intracellular calcium. Part of the basis for this was the work of Schanne and colleagues (1979), who showed that certain agents were able to cause toxic cell death in cultured rat hepatocytes only if Ca_e was normal. If Ca_e was reduced to the level of normal intracellular calcium activity, these agents had no effect.

The Hass hypothesis suggests that increased intracellular calcium activity would stimulate breakdown of the phosphatidylinositol pool with serious consequences for neurotransmitter metabolism during reperfusion. Increased intracellular calcium activity would also stimulate phospholipase A2 activity with release of free fatty acids. A major free fatty acid released would be arachidonic acid, the precursor of the prostaglandins and other related substances which may have further deleterious effects upon ischaemic cerebral tissue.

The relationship of flow to tissue viability

In many animals the somatosensory evoked response is abolished by middle cerebral occlusion without added hypotension. It is particularly interesting to note that the area of functionally suppressed cortex is much wider than the area of cortex which will proceed to infarction in chronic experiments, a group of comparable animals having been maintained over 3 years while the characteristics of their clinical stroke were studied. Detailed pathological studies with perfusion fixation have been performed by Brierley and Symon (1977), and show that infarction is confined to areas where blood flow reduction in the acute stage of the stroke is certainly below values of 10 ml min^{-1}/100 g. In the acute stage of infarction, loss of function affects neurones in a much wider distribution than the ultimate structural loss. In accordance with this view, Morawetz and others (1978) found that histopathological signs of structural infarction following a 2–3 h period of focal ischaemia in the monkey were obtained only at sites where local blood flow was less than 10–15 ml min^{-1}/100 g.

From these observations, we developed a concept that an area of structural loss in stroke was probably surrounded for some time, in the acute phase, by an area of functional neuronal suppression, in which the structural integrity of the neurones was immediately, and even permanently, preserved. This we termed the "ischaemic penumbra". We now have some evidence that in the penumbral areas, some basic physiological mechanisms of the neurone remain intact, particularly those concerned with ionic homeostasis at the cell membrane level. In our experiments, control concentrations of extracellular potassium ranging from 3 to 9 mmol (mean 5.7 ± 1.5) were maintained with only minor changes at approximately the value of the threshold for electrical function, but significant and massive movements of potassium ion into the extracellular space occurred when flow decreased to between 7 and 11 ml min^{-1}/100 g, significantly less than the value for failure of electrical function. It is postulated, therefore, that there is a differential failure of neuronal metabolic processes so that, in the penumbral area, synaptic transmission is impaired but the energy state and the ionic balance are maintained at normal values. Presumably, the metabolic rate of oxygen is reduced to a minimum by the arrest of function. Some support for this view has come from studies of Siesjö and his group in bicuculline-induced status epilepticus, where it has been found that, during progressive ischaemia and failure of seizural activity, the tissue content of ATP is maintained at near normal values until the point at which potassium is massively released from the cells.

Neurotransmitter function

In collaboration with Davison and Bowen (Bowen et al., 1976) we have attempted to link the degree of ischaemia to the function of subcellular components, particularly neurotransmitter uptake by synaptosomes. Current evidence suggests that the synaptosomal uptake of the neurotransmitter GABA shows a linear decline in relation to flow, which probably commences at a flow greater than that required to interfere with electrical function. Cholinergic neurones however, show no such sensitivity, and uptake remains unimpaired to very much lower values.

Water movement

Studies from our laboratory (Symon, Branston and Chikovani, 1979) and from Hossmann and Schuier (1978), have indicated a definite relationship between the development of cerebral swelling and the intensity of brain ischaemia. In our experimental model, we assessed brain water content in life by brain impedance measurements and intracranial pressure changes, and following the sacrifice of the animal by the use of graded density kerosene bromobenzene columns. We found that significant ischaemia was associated, at 1.5 h, with an increase in water content in the most densely ischaemic zones and in the area of the penumbra. Movement of water occurred when flow decreased to less than 20 ml min^{-1}/100 g, and it appears to be the initial depth of ischaemia which acts as a trigger mechanism, releasing water which thereafter advances through the hemisphere as described for cold oedema fronts by Reulen and colleagues (1977).

After 1.5 h of ischaemia, reperfusion is associated with an increase rather than a decrease in ischaemic oedema. Restoration of blood flow after a significant period of ischaemia may thus compound the problem of brain swelling. The flows necessary to evoke brain swelling are significantly greater than those concerned with impairment of cell membrane permeability. Impairment of vascular permeability to large molecules is unlikely to be the cause, since there is clear evidence that such vasogenic brain oedema generally develops only after 4–6 h and reaches its maximum after a few days. Leakage of large molecules such as per-technetate or RIHSA is maximal in an ischaemic stroke only after 10 days to 3 weeks. O'Brien, Waltz and Jordan (1974) have observed an increase in water content of cortex of up to 90%, a few days after experimental stroke. It seems probable that such oedema is an accompaniment to tissue necrosis, since it does not seem to be evoked by vascular occlusion of less than 6 h duration, which would be expected (from the work of Morawetz) to produce significant tissue loss.

We should therefore regard the early phase of brain oedema as cytotoxic rather than vasogenic. Our observations and those of Hossmann indicate that the degree of this type of oedema is determined by the initial flow reduction after vascular occlusion. Hossmann has also shown that, following 1 h of complete ischaemia, there is a significant increase in tissue osmolality, from 308 to 353 mosmol, creating a gradient of about 50 mosmol between brain and blood (Hossmann and Takagi, 1976). It may well be that the correspondence of the level of ischaemia necessary to evoke brain swelling, and the approximate level necessary to abolish brain function, indicates an increase in osmolality associated with failure of synthesis of large neurotransmitter molecules, their smaller precursors being allowed to remain free, and thereby significantly increasing osmolality.

Reperfusion and recovery

These studies have shown that, under widely varying conditions of focal ischaemia, including, in some areas, reduction of blood flow sufficient to produce a significant release of potassium ions into the extracellular space, recovery of potassium concentration toward control values usually occurs upon reperfusion. Complete failure of potassium to decrease was noted only at one electrode site in a total of 29. Recovery to within control confidence limits occurred in approximately 50% and followed significantly greater density and duration of ischaemia than incomplete recovery. Significantly higher reperfusion flows also attended complete recovery, reflecting probably the condition of the ischaemic phase.

The rate of recovery did not correlate significantly with the duration of occlusion by arterial clip, with minimum flow during clip, or with the maximum potassium concentration recorded during the clip. However, it correlated inversely ($r = 0.5$, $P < 0.04$) with the total time during the clip phase for which the site was exposed to flows of less than 10 ml min^{-1}/100 g. Although chosen arbitrarily, this flow threshold is similar to that at which significant increases in potassium activity are first seen during progressive ischaemia (Branston, Strong and Symon, 1977). We have termed the time variable, thus defined, the flow deficit associated with that site (units: minutes). Once again, the slow component of biexponential clearance of ECF K^+ did not appear to depend on the flow deficit, since the regression slope was zero.

When the MCA is occluded under the experimental conditions described, the degree of ischaemia in a given region determines whether or not the EP is significantly depressed there. Severe electrophysiological depression, often to a very small fraction of control, occurs when the local blood flow decreases below a critical value of approximately 16 ml min^{-1}/100 g, as established previously (Branston et al., 1974) and shown also in data derived from the monitoring of EEG and flow over wider brain areas with less localization (Sharbrough, Messick and Sundt, 1973; Trojaborg and Boysen, 1973); additional corroborative data at the level of individual cortical neurones has been presented by Heiss, Waltz and Hayakawa (1975). Our data indicate further that, if this degree of ischaemia is maintained for longer than 15 min incomplete recovery of the EP occurs in the post-clip phase, at least over the period of 1 h or so following removal of the clip. During this period, the local blood flow has been restored, but tissue $P\text{O}_2$ remains reduced (on average) to values well below control.

The effects of drugs

In recent years there have been a number of attempts to influence focal ischaemia by a variety of pharmacological means. Several experimental models have suggested the possibility that barbiturates may exert a protective action in the ischaemic brain. Reduction in infarct size, reduced neurological deficit and increased survival time following stroke (Yatsu et al., 1972; Smith et al., 1974; Wright and Ames, 1974; Hoff et al., 1975; Michenfelder, Milde and Sundt, 1976; Bleyaert et al., 1977; Flamm et al. 1977; Corkill et al., 1978; Crane et al., 1978) have been suggested with both pre- and post-insult administration of the drug. As Michenfelder and Milde (1975) have pointed out, extending these models to clinical trials in order to assess the protective effects of barbiturates in the treatment of acute stroke may be difficult, chiefly because of the haemodynamic and pulmonary complications accompanying the anaesthetic effect of the drugs given in the doses suggested by experiment.

We have studied the effects of two i.v. barbiturates, pentobarbitone and methohexitone, each of which has been suggested to afford protection in cerebral ischaemia (Yatsu et al., 1972; Smith et al., 1974; Wright and Ames, 1974; Hoff et al., 1975; Michenfelder and Milde, 1975; Michenfelder, Milde and Sundt, 1976; Bleyaert et al., 1977; Flamm et al., 1977; Corkill et al., 1978; Crane et al., 1978) on the distribution of blood flow in the cerebral cortex after occlusion of the middle cerebral artery. We have also assessed their effects on the threshold relationship between flow and neuronal function as exemplified by the cortical evoked response, and on the ionic homeostasis assessed by extracellular potassium activity (Branston et al., 1974; Branston, Strong and Symon, 1977), comparing the flow threshold relationships with those obtained in control experiments without barbiturate.

We assessed the effects of methohexitone or pentobarbitone pre-loading before middle cerebral occlusion, and of methohexitone following middle cerebral occlusion (Branston, Hope and Symon, 1979) and found that barbiturates significantly depressed hemispheral blood flow in the control phase from initial slope values of 68 ± 23 ml min^{-1}/100 g to 38 ± 15 ml min^{-1}/100 g ($P < 0.001$) with a concomitant small decrease in systemic arterial pressure and also significantly decreased extracellular potassium activity. In parallel with this, EP amplitude decreased in the control phase and there was a significant correlation between the reduction of amplitude of the primary evoked response and a reduction in cortical blood flow.

Following middle cerebral occlusion, flow depression induced by barbiturate depended on the degree of ischaemia present initially in that region. There was a flow-homogenizing effect of barbiturate, higher flows being reduced more than lower flows, and it was of interest that flow was depressed by the barbiturate only down to the EP threshold, electrical activity was abolished by the initial ischaemia in the given region, and barbiturate did not reduce the flow further. This indicated that the barbiturate was acting, not by direct action on the vessel wall, but indirectly by reduction of electrical activity and metabolic rate.

There was no evidence that barbiturate loading had in any way altered the relationship between flow and massive efflux of potassium, although during methohexitone protection massive K_e increases in ischaemia occurred at flows of approximately 8–9.5 ml min^{-1}/100 g where chloralose was the sole anaesthetic. This was not a significant protective effect on the barbiturate thresholds and our conclusion was that preservation of the membrane ion pump to maintain normal K_e values was not an important factor in barbiturate protection. We drew similar conclusions regarding the threshold of failure of the evoked response. The data did, however, illustrate that, once EP had started to diminish in amplitude, the rate of amplitude decrease for a given steady-state flow value was less in methohexitone protection in comparison with the rates found in the control studies where chloralose alone was used. We considered that this might indicate a reduction of the rate of depletion of synaptically-based metabolites and local metabolic consumption of oxygen by methohexitone (Guiditta, 1962; Pierce et al., 1962; Guiditta and Di Prisco, 1963) analogous to the reduced rate of increase of K_e found by Astrup, Nordström and Rehncrona (1977). This effect was not found with pentobarbitone in our experimental format, possibly because it has less lipid solubility and therefore less cell penetration than methohexitone.

It was of interest that methohexitone produced a significant increase of flow in regions of cortex where flow following MCA occlusion was below the EP threshold provided that arterial pressure remained steady. The increase, though small, averaged 3.4 ml min^{-1}/100 g and was statistically significant and a substantial fraction of the post-occlusive pre-methohexitone treatment flow. We postulated that this indicated an inverse steal flow from relatively well perfused cortical regions following the reduction in metabolic rate and possibly vasoconstriction induced by the barbiturate, with diversion into relatively ischaemic regions where the barbiturate influenced metabolism and vessel wall rather less. Such an inverse steal would enlarge the size of the viable region of brain in which electrical activity had been silenced, but in which irreversible structural damage had not occurred (Astrup, Siesjo and Symon, 1981), and thus would tend to reduce the size of the developing infarct.

Attempts to influence cerebral oedema

Prostaglandins have been implicated in the pathophysiology of ischaemic cell damage and increased outflow of prostaglandins from hypoxic brain (Ruszczewski, 1978) is well-known. Indomethacin, a potent inhibitor of prostaglandin synthesis (Abdel-Halim, Sjoquist and Anggarde, 1978; Monada and Vane, 1979), when given pre-insult, has been shown to aid post-ischaemic reperfusion (Hallenbeck and Furlow, 1979) and improve the quality of recovery of gerbils subjected to transient bilateral common carotid occlusion (Gaudet and Levine, 1979). These observations support the proposal that metabolites such as arachidonic acid are involved in the pathophysiology of cerebral ischaemia (Yamamoto, 1972; Wolfe and Coceani, 1979), although indomethacin has been shown to increase the size of myocardial infarcts in dogs (Jugdutt et al., 1979).

We have investigated the effects of indomethacin pre-loading on our experimental infarct preparation, assessing oedema information by specific density columns, blood flow by hydrogen clearance and ionic homeostasis by extracellular measurements of potassium and calcium. Indomethacin significantly decreased flow in control circumstances by approximately 40% relative to the initial flow and reduced carbon dioxide reactivity by approximately 70%. Indomethacin had no effect on the blood flow recorded after middle cerebral occlusion. However, the water content of the ischaemic hemisphere was always greater than that in untreated animals and indomethacin increased the flow threshold for potassium and calcium movements significantly, from approximately 12 ml min^{-1}/100 g to 17 ml min^{-1}/100 g for potassium and from approximately 6–8 ml min^{-1}/100 g for calcium to 11 ml min^{-1}/100 g for the indomethacin treatment. The relationship between indomethacin and potassium remained the same.

Our results therefore confirmed the findings o Pickard and others (1980) that indomethaci reduced normocapnic blood flow and carbo dioxide reactivity. The effects on water conten suggested that, while indomethacin did not alte normal brain water content, water content values fo all ranges of blood flow greater than 0-5 ml min^{-1}/100 g were increased after indomethacin. This accords with the absence of effect o indomethacin on the production of oedema b increasing arachidonic acid concentration (Chan an Fishman, 1978).

Interest in the Hass hypothesis (1981) on th mechanism of potential cell death, prompted us t examine the use of calcium antagonists (nimodipine (Kazda et al., 1979) which have been shown to hav a selective effect on cerebral vessels and to improv the post-ischaemically impaired flow in cats following 7 min of total cerebral ischaemia. In our standar model, we compared the effect of nimodipine infusion on carbon dioxide reactivity and autoregulation, demonstrating that carbon dioxide reactivit was decreased significantly, to approximately 50%

of normal, by nimodipine infusion while nimodipine significantly increased basal blood flows in all areas of the primate cortex. Interestingly, there was no significant difference between the reactivity of the vessels to either hypercapnia or hypocapnia, although one might have expected its competitive vasodilatation would have influenced only the carbon dioxide vasodilator response (Harper, 1965; Carter and Atkinson, 1973). After middle cerebral occlusion, residual blood flow with nimodipine infusion was significantly increased. This is consistent both with the demonstration by Ott and Lechner (1980) that oral nimodipine caused redistribution of blood flow in an infarcted hemisphere, and with the suggestion that an increase in collateral circulation is the mechanism of protection in myocardial ischaemia with calcium antagonists (Bing, 1980; Gross et al., 1980; Poole-Wilson, 1980).

Infusion of nimodipine did not affect osmoregulation in the non-ischaemic tissue, but when blood flow was decreased in treated animals, water stimultion was significantly greater than that observed previously in untreated animals. Blood flow thresholds for the disruption of K_e and calcium homeostasis were also increased by nimodipine treatment. The increase in K_e in ischaemia almost certainly resulted from increase in potassium permeability, but since there was no change in K_e or Ca_e when the drug was infused, it seems that, if there was an increased susceptibility of cellular energy metabolism it occurred only in association with ischaemic damage. There are no biochemical data supporting this.

Nimodipine produced an impairment of autoregulation to reduced arterial pressure, a finding consistent with pre-dilatation of the vascular bed, as might be expected with a calcium antagonist. However, there was much less effect of nimodipine on autoregulation to increased arterial pressure, indicating that ability of vessels to constrict was unaffected.

It seemed, therefore, that nimodipine may have both beneficial and deleterious effects in relation to ischaemia. The drug considerably impaired cerebral artery responses to alterations in arterial $P\text{CO}_2$ and haemorrhagic hypotension, it impaired the critical level of blood flow for oedema formation and for destruction of ionic homeostasis, whilst it did not inhibit the decrease in extracellular calcium during ischaemia. However, it did increase the immediate post-occlusion flow two-fold in an experimental infarct, and this effect would tend to maintain blood flow above the thresholds of loss of electrical activity, ionic homeostasis and the formation of ischaemic oedema in the recovery period.

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ISCHAEMIC BRAIN DAMAGE: THE ROLE OF EXCITATORY ACTIVITY AND OF CALCIUM ENTRY

B. MELDRUM, M. EVANS, T. GRIFFITHS AND R. SIMON

The pattern of selective vulnerability occurring after cerebral ischaemia is similar to that after status epilepticus (Brierley, 1976; Corsellis and Meldrum 1976). In the hippocampus, the pyramidal neurones in the CA1 and CA3 zones and the hilar polymorphic neurones are particularly vulnerable and the dentate granule cells are relatively resistant. During status epilepticus induced experimentally in rats by the i.v. administration of bicuculline, allylglycine or kainic acid (Evans, Griffiths and Meldrum, 1983, 1984; Griffiths, Evans and Meldrum, 1983, 1984), selectively vulnerable neurones show condensation of perikaryal cytoplasm and swelling of mitochondria. The changes are evident after 30–90 min of continuous seizure activity. Severe condensation with a pyknotic nucleus and multiple, small, structureless vacuoles occur in a minority of vulnerable neurones after 90–150 min (Evans, Griffiths and Meldrum, 1984; Griffiths, Evans and Meldrum, 1984).

The oxalate–pyroantimonate method for the electron microscopic visualization of calcium reveals massive calcium deposits in swollen mitochondria, both in focal dendritic swellings and in the perikaryal region (Griffiths, Evans and Meldrum, 1984). We have compared the acute changes in status epilepticus with those seen during reperfusion after 30 min of forebrain ischaemia (Simon, Griffiths et al., 1984). The similarity in the changes suggests that enhanced activity, probably taking the form of burst firing in vulnerable neurones, contributes to the pathological outcome.

Adult Wistar rats, prepared under halothane anaesthesia and maintained on nitrous oxide–oxygen, were peripherally paralysed and snares placed round the common carotid arteries. After a period of stabilization, the arteries were occluded and the mean arterial pressure was reduced to 50 mm Hg. After 30 min, flow was restored and mean arterial pressure maintained at 100–120 mm Hg. The brain was perfusion-fixed with a modified Karnovsky's solution containing 2% paraformaldehyde, 2.8% glutaraldehyde and potassium oxalate 90 mmol litre^{-1}. Vibratome slices of dorsal and ventral hippocampus were washed in 7.5% sucrose containing potassium oxalate 90 mmol litre^{-1}. The modified pyroantimonate technique for precipitating calcium as calcium pyroantimonate was performed (Borgers, Thone and Van Neuten, 1981), and slices were embedded in araldite, cut at 50–80 nm and stained with uranyl acetate and lead citrate.

After 30 min ischaemia and no reperfusion, hippocampal neurones showed normal ultrastructural morphology except for clumping of nuclear chromatin. This was observed equally in pyramidal neurones and dentate granule cells and probably reflects the intracellular acidosis associated with ischaemia. Occasional neurones showing swollen mitochondria with dense calcium pyroantimonate deposits were apparently indicative of partial ischaemia, that is, a focally maintained minimal flow permitted the accumulation of calcium.

After 30 min of reperfusion, cytopathology was severe and generalized, affecting pyramidal neurones and dentate granule cells equally. Nuclear outlines were irregular and the density of the cytoplasm was increased. In nearly all neurones there were swollen disrupted mitochondria containing dense calcium pyroantimonate deposits. Swollen astrocytic processes occurred throughout the pyramidal cell layer and hilar region.

After 2 h reperfusion, a pattern of selective pathology was evident. Dentate granule cells were uniformly normal in morphology. Pyramidal neurones showed marked variation, some appearing

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essentially normal, others showing "ischaemic cell change", with severe condensation obliterating fine structural detail except for multiple vacuoles containing calcium deposits (fig. 1). Ischaemic cell change was commonest in pyramidal cells in CA_1 (adjacent to the subiculum) and in basket cells and polymorphic neurones in the hilar region. Focal dendritic swellings containing swollen mitochondria with dense calcium deposits were evident in the distal parts of the basal dendrites of CA1 and CA3. Such focal swellings nearly always showed one or more asymmetric (excitatory) synaptic terminals. These appearance were closely similar to those seen after 90 min of seizure activity (fig.2).

Evidently, the movement of calcium from the extracellular space into neurones during the first minutes of ischaemia (Harris et al., 1981) does not lead to intracellular calcium deposits that are visualized by this method. However, during reperfusion, extracellular calcium is replenished and mitochondrial oxidative metabolism re-established so that, with only partial repolarization of the plasma membrane or burst firing, calcium enters neurones and is accumulated actively by mitochondria. This occurs non-selectively in the first 30 min of reperfusion. Subsequently, normal resting potentials are restored and outward transport of Ca^{2+} by membrane Ca–Mg ATPase brings cytosolic $[Ca^{2+}]$ to normal values, allowing efflux of Ca^{2+} from mitochondria, However, in some selectively vulnerable neurones, burst firing in the subsequent 90 min leads to a continued accumulation of Ca^{2+}.

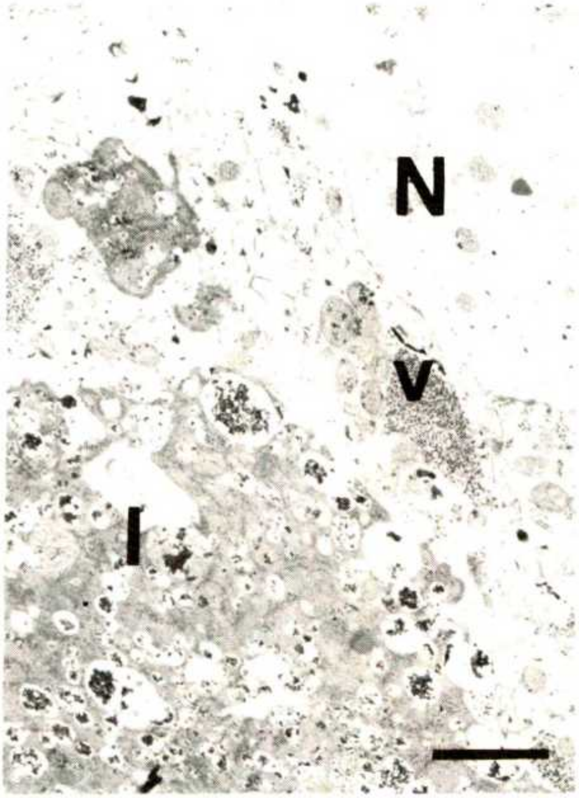

FIG. 1. Electron micrograph of CA1 region of the hippocampus in a rat after 30 min ischaemia and 120 min reperfusion. N = normal neurone; v = nerve terminal packed with vesicles containing calcium pyroantimonate deposits (a normal appearance); I = neurone showing ischaemic cell change; multiple vacuoles contain calcium pyroantimonate deposits. Bar indicates 1 μm.

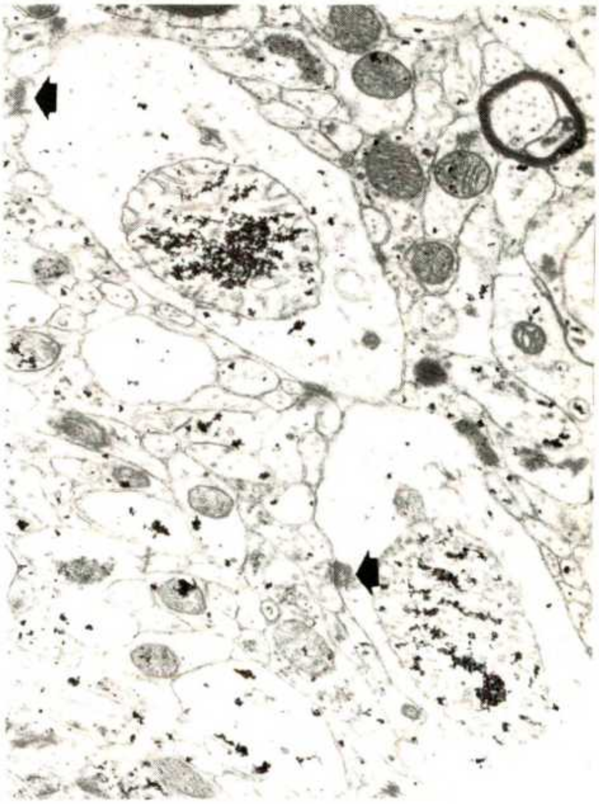

FIG. 2. Electron micrograph of stratum oriens in CA3 region of hippocampus in a rat after 90 min of seizure activity. Focal dendritic swellings contain grossly swollen mitochondria with dense calcium pyroantimonate deposits. Synaptic terminals making excitatory (asymmetric) contacts are identifiable in relation to the focal swellings (arrowheads). Similar changes are found after 30 min ischaemia and 2 h recovery (Simon et al., 1984).

Evidence for a role of excitatory transmitters acting on a particular sub-class of receptors has been provided in a further series of experiments with similar ischaemic and reperfusion periods. 2-similar ischaemic and reperfusion periods (Simon, Swan et al., 1984). 2-Amino-7-phosphonoheptanoic acid is a specific antagonist of excitation at the "N-methyl-D-aspartate receptor" and is a potent anticonvulsant agent (Meldrum et al., 1983). A chronically implanted guide tube permitted the focal injection of 2-amino-7-phosphonoheptanoic acid (20 µg in 1 µl) into one dorsal hippocampus immediately before the ischaemic episode. The brain was perfusion fixed after 30 or 120 min of reperfusion, and hippocampal blocks embedded in paraffin and serially sectioned for light microscopy.

The pathological changes were similar to those observed in the study described above, except that the injection of buffer solution appeared to delay recovery in the dentate granule cells so that, at 120 min, some of these still showed dark staining. In the hemisphere receiving 2-amino-7-phosphonoheptanoic acid, the hippocampus showed little or no pathological abnormality at 120 min, in dramatic contrast to the buffer-injected side. The protection involved all cell types within a sphere of 1–2 mm surrounding the injection site and on occasion protection of pyramidal neurones extended more anteriorly and posteriorly within the hippocampus. This protective action of 2-amino-7-phosphonoheptanoic acid implies that excitation at the "N-methyl-D-aspartate preferring receptor" plays an important part in determining the appearance of ischaemic cell change. Agonists at the NMDA-preferring receptor activate a membrane calcium conductance (Dingledine, 1983) and induce paroxysmal burst firing (Herrling, Morris and Salt, 1983). Spread of burst firing from CA3 neurones to CA1 neurones depends on an excitatory amino acid transmitter released by the Schaffer collaterals. It appears that suppression of burst firing during the recovery period by blocking one class of excitatory receptor site prevents excessive calcium entry and thereby protects against the acute occurrence of ischaemic cell change. These observations provide a novel therapeutic approach to cerebral ischaemia.

ACKNOWLEDGEMENT

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CEREBRAL METABOLISM IN ISCHAEMIA: NEUROCHEMICAL BASIS FOR THERAPY

B. K. SIESJÖ AND T. WIELOCH

It seems obvious to assume that the density of ischaemic brain damage, if incurred, is related to both the severity and duration of cerebral ischaemia. As a corollary, only the duration of ischaemia should determine the outcome if ischaemia is complete, that is, if nutritional blood flow has ceased completely. However, such postulates are only partly true, for several reasons.

First, evidence exists that unless cerebral blood flow (CBF) is decreased below a certain threshold value, neuronal damage will not develop, even if ischaemia is prolonged. Second, under certain circumstances, brief periods of ischaemia may cause surprisingly extensive damage. This may, for example, occur with inadequate restoration of post-ischaemic cerebral perfusion pressure, a condition in which ischaemia is extended into the recirculation period. Another possible cause of secondary damage is post-ischaemic seizure activity.

Third, it is now clear that, for a given density and duration of ischaemia, the outcome depends critically on the cerebral metabolic reaction to the failing circulation. Thus, although ischaemia is a disease of the cerebral circulation, its impact on the tissue is determined by neurochemical events at the cellular and subcellular level.

The purpose of this article is to review these events, to discuss their relative importance, and to speculate on therapeutic measures which may curb their ill effects. By necessity, the description must be selective and the quotations restricted to reviews and a few original articles. For further details, and additional references, the reader is referred to recent review articles (Siesjö, 1981, 1984a; Hossmann, 1982; Siesjö and Wieloch 1984a, b).

METABOLIC CASCADES IN ISCHAEMIA

In this section are posed three questions. First, what is the rate of catabolic reactions if cerebral circulation suddenly ceases completely? Second, in what order are these reactions elicited if CBF is decreased gradually? Third, is it possible to identify, at least provisionally, one or several reactions which represent the first steps on the road from which there may be no return? Neurochemical events during ischaemia exhibit a dual relationship to fluxes of ions across cellular and subcellular membranes. On one hand, deterioration of cellular energy state causes dissipative ("downhill") fluxes of ions. On the other hand, influx of ions (e.g. Ca^{2+}) to cells modulates or initiates catabolic reactions which, unless prevented or arrested, may cause membrane dysfunction and cell death. Since ion fluxes associated with ischaemia are reviewed elsewhere in this Symposium, only those aspects which are relevant to intracellular metabolic events are discussed here.

Sudden, total ischaemia

No doubt, the most important events are those leading to cessation of energy production, and the non-availability of energy stores. As figure 1 shows, these events are rapid. Thus, significant decreases in phosphocreatine (PCr) and ATP concentrations, and significant increases in ADP, AMP and lactate concentrations, occur within 10 s. Complete energy failure, as reflected in a decrease of the adenylate energy charge to minimal values, ensues within 5–7 min. Normal pre-ischaemic stores of glucose and glycogen suffice to increase tissue lactate content from approximately 1.5 to 12–14 μmol g^{-1}, an event which occurs during the first 2–3 min (Ljunggren, Norberg and Siesjö, 1974). With this degree of lactic acidosis, intracellular pH (pH_i) can be estimated to decrease from approximately 7.0 to approximately 6.4. However, the lactate values

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obtained depend on the nutritional state, notably on blood glucose concentrations (Ljunggren et al., 1974). Thus, when pre-ischaemic blood-glucose concentrations were set at 2.4 (hypoglycaemia), 7.8 (normoglycaemia), and 28 (hyperglycaemia) μmol ml^{-1}, the ischaemic tissue lactate concentrations were 4.8, 12.1, and 20.7 μmol g^{-1} respectively. For these groups, calculated tissue $P\text{CO}_2$ and pH were as shown in table I. We note that, since carbon dioxide is trapped in tissue, lactic acidosis causes $P\text{CO}_2$ to increase precipitously. Clearly, there is a relationship between blood (and tissue) glucose concentration, accumulation of lactate, and acid–base changes.

At this point, it should be emphasized that the presence of some remaining flow during ischaemia provides a source of exogenous glucose. In starved animals, which do not develop hyperglycaemia during ischaemia, this does not cause lactate content to increase above values recorded in normoglycaemic

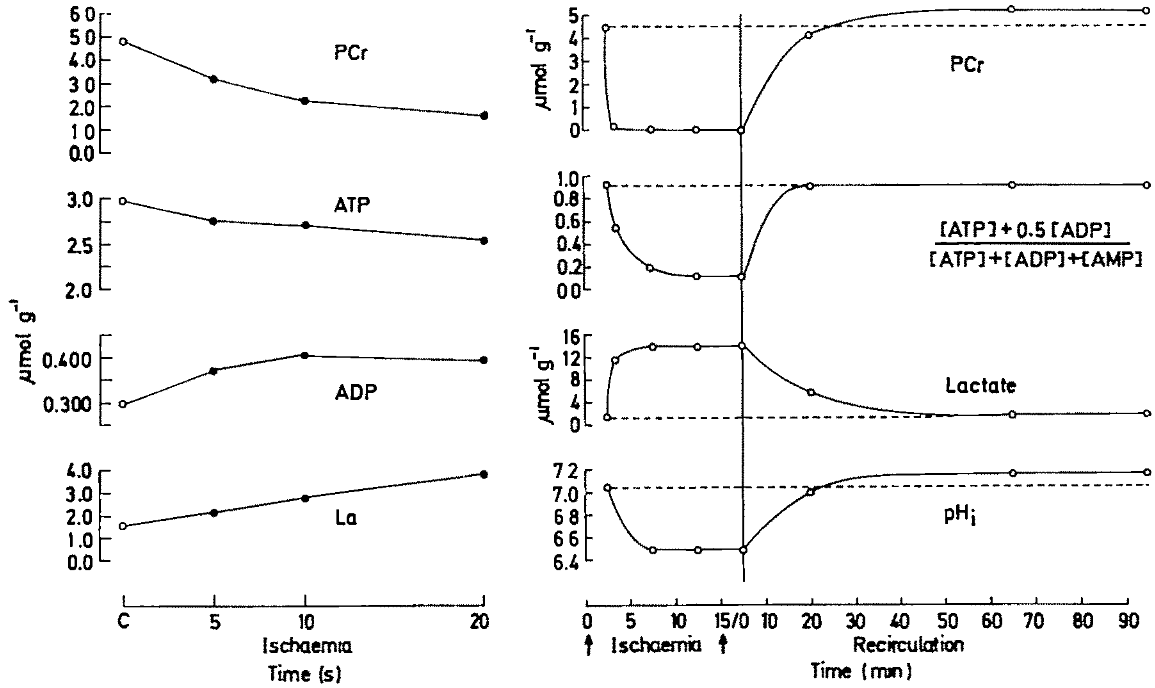

FIG. 1. Energy failure and loss of acid–base homeostasis during ischaemia. The left panel illustrates changes in labile phosphates and lactate content of rat cerebral cortex during complete ischaemia of 20 s duration. Filled circles denote values significantly different from control ($P < 0.05$). (Data from Nilsson and colleagues (1975).) The right panel denotes corresponding changes during and following complete ischaemia of 15 min duration, with values for calculated intracellular pH included. (Modified after Siesjo (1984a).) PCr = phosphocreatine; La = lactate.

TABLE I. *Calculated tissue* PCO_2 *and pH for different amounts of intracellular lactic acid formed during ischaemia in hypo-, normo-, and hyperglycaemic animals*

Group	Increase in lactate (μmol/g tissue water)	Tissue $P\text{CO}_2$ (kPa)	Tissue pH
Hypoglycaemia ($n = 4$)	4.4 ± 0.9	8.6 ± 0.66	6.83 ± 0.04
Normoglycaemia ($n = 4$)	13.8 ± 0.6	17.5 ± 0.66	6.42 ± 0.03
Hyperglycaemia ($n = 4$)	20.7 ± 0.4	28.3 ± 1.2	6.05 ± 0.04

animals with complete ischaemia. However, feeding or glucose-infusion allows plasma glucose concentrations to increase and, under these conditions, tissue lactate values may reach excessive values, sometimes exceeding 30 μmol g^{-1}, with a resulting decrease in pH to very low values (Siesjö, 1984b; Siesjo and Wieloch, 1984a, b). The pathophysiological importance of such excessive acidosis is considered further in a following section.

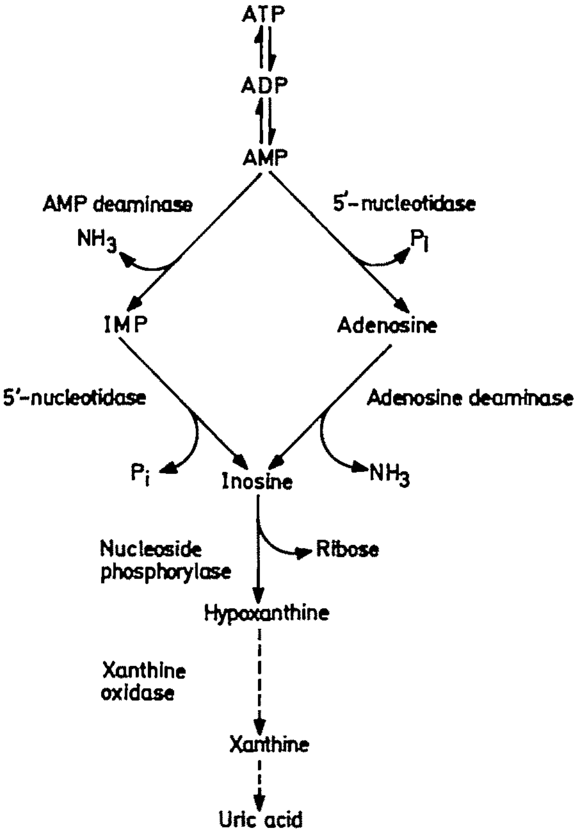

FIG 2. Schematic diagram illustrating dephosphorylation and deamination of AMP, with accumulation of adenosine, AMP, inosine and hypoxanthine. In the brain, xanthine oxidase activity seems insufficient to cause oxidation of hypoxanthine to xanthine (stippled lines). (Reproduced with permission from Siesjo and Wieloch (1984b).)

As figure 2 shows, degradation of ATP to AMP allows the latter to be dephosphorylated to adenosine and deaminated to IMP, and these two degradation products of AMP are subsequently converted to inosine and hypoxanthine (Kleihues, Kobayashi and Hossmann, 1974; Chapman, Westerberg and Siesjö, 1981). As a result of these spontaneous reactions, the sum of adenine nucleotides (ATP + ADP + AMP) is reduced. Recirculation does not allow immediate resynthesis of nucleotides, since some of the degradation products may be lost from the circulation, and also synthesis by kinase activity or by *de novo* pathways is slow (Chapman, Westerberg and Siesjö, 1981). Thus, although the energy charge of the remaining nucleotide pool may be normalized quickly, ATP concentrations may remain reduced for several hours. Another consequence of the degradation of AMP is accumulation of hypoxanthine, the substrate of xanthine oxidase. Although this reaction is a potential source of free radicals, it does not seem to be activated in brain tissues, and it remains to be shown that it could trigger free radical damage.

Provided that ischaemia is of moderate duration and that an adequate perfusion pressure can be restored, recirculation produces rapid normalization of the phosphocreatine (PCr) concentration and the energy charge of the adenine nucleotide pool. In fact, the PCr concentration overshoots the control value, reflecting the influence of intracellular alkalosis on the creatine kinase equilibrium.

The intracellular alkalosis is probably the result of the combined extrusion of H^+, fuelled by ATP energy, and oxidation of lactate accumulated during ischaemia (Mabe, Blomqvist and Siesjo, 1983; Siesjö, 1984b). We wish to emphasize, though, that if ischaemia is of longer duration or the post-ischaemic perfusion pressure is inadequate, or both, normal mitochondrial function is not resumed, and the acidosis is not reversed.

As a result of the depletion of energy reserves, cell membranes are depolarized. This, in turn, is associated with (and partly caused by) dissipative ion fluxes, with release of K^+ from, and uptake of Ca^{2+}, Na^+ and Cl^- into cells (fig. 3). Soon after cessation of flow, extracellular K^+ (K_e^+) increases gradually until, after 1–2 min, K^+ floods into extracellular fluid (Hansen and Zeuthen, 1981; Harris et al., 1981). The slow initial increase may result from relative energy failure at the site of the membrane-bound ATPase, and the subsequent, fast release from gross cellular energy failure. Sudden influx of Ca^{2+} occurs when K_e^+ increases to 10–15 μmol ml^{-1}, possibly because of opening of voltage-dependent Ca^{2+} gates (Harris et al., 1981). Since there is also a marked reduction of extracellular fluid (ECF) volume, one must conclude that Na^+ and Cl^- are taken up by cells with osmotically dependent water. Probably, uptake of Ca^{2+} occurs predominantly into neurones while the major amounts of Na^+ and Cl^- enter glial cells. This issue is further discussed below.

There is a wealth of information demonstrating that these events (notably membrane depolarization and Ca^{2+} influx) cause release of established and putative neurotransmitters, including excitatory amino acids, catecholamines, and adenosine. Release of vesicle-bound transmitters is one event elicited by Ca^{2+} influx. Release of excitatory amino acids may, in turn, enhance Ca^{2+} influx into post-synaptic elements (see below). Egress of adenosine could occur by a similar mechanism, that is, by release of ATP and its subsequent conversion by ectoenzymes to adenosine (Burnstock, 1980). However, massive amounts of adenosine are also formed intracellularly when ATP is broken down to ADP and AMP, the latter being converted to adenosine by 5′-nucleotidase (fig. 2). Clearly, energy depletion triggers a cascade of reactions in which depolarization, dissipative ion fluxes, and release of agonists occur, and which sets the stage for excessive stimulation of membrane receptors.

Cessation of oxygen supply arrests all anabolic reactions and allows catabolism to proceed unabated. Although this applies to proteins, it has been shown that some catabolic reactions, for example disaggregation of polyribosomes, do not occur until (and if) oxygen is resupplied (Cooper et al., 1977; Dienel, Pulsinelli and Duffy, 1980). One conspicuous event is that affecting the free fatty acid (FFA) pool of tissue (fig. 4). As originally shown by Bazan (1970), ischaemia leads to rapid accumulation of FFA, especially the polyunsaturated arachidonic acid. Subsequent studies have shown that the FFA, including arachidonic acid, continue to accumulate even if ischaemia is prolonged, and that recirculation produces relatively slow disappearance of the FFA accumulated (Yoshida et al., 1980; Rehncrona et al., 1982). As discussed below, this allows oxidative conversion of FFA in the immediate recirculation period, either by non-enzymatic routes or in

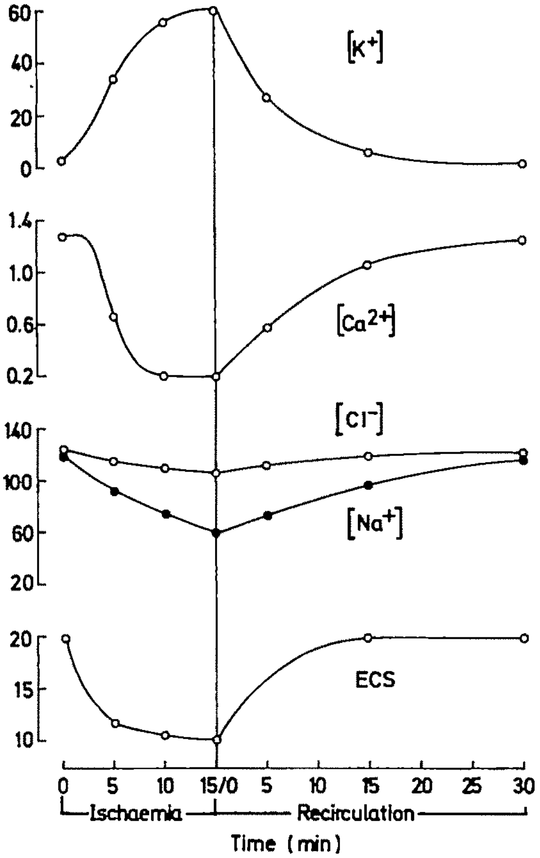

FIG 3. Schematic diagram illustrating changes in cerebral extracellular concentrations of K^+, Ca^{2+}, Cl^-, and Na^+, (μmol ml^{-1}), and also in extracellular fluid space (ECS) (percent of brain weight) (Slightly modified after Siesjo and Wieloch (1984b).)

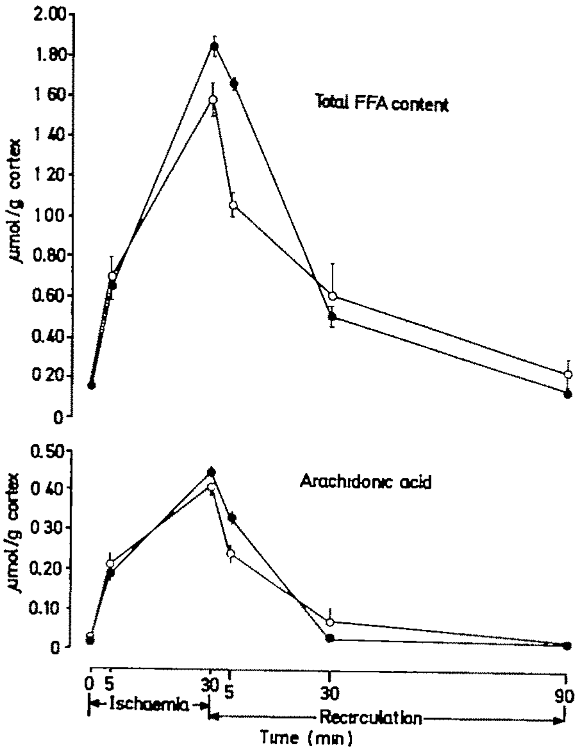

FIG 4 Influence of transient ischaemia on total free fatty acid content, and arachidonic acid concentration, of cerebral cortex. ● = Complete ischaemia; ○ = severe, incomplete ischaemia. (Slightly modified after Siesjo and Wieloch (1984a).)

reactions catalysed by cyclo-oxygenase and lipoxygenase.

Gradual reduction of flow—metabolic thresholds

Information on critical ischaemic thresholds is extensive, but incomplete. Thus, although thresholds for "electrical" failure and "ion pump" or "membrane" failure have been defined (Astrup, Siesjö and Symon, 1981; Astrup, 1982; Symon, 1985) the metabolic counterparts are less well known. Below the electrical threshold, synaptic transmission and spontaneous electrical activity are depressed. With a further reduction in flow, the threshold of membrane failure is reached, heralded by dissipative ion fluxes. Clearly, failure of neurophysiological functions must have a neurochemical basis, but mechanisms have proved elusive. At present, one can only speculate that reduction of oxygen availability interferes in some way with the orderly synthesis or release, or both, of neurotransmitters necessary to support normal cell-to-cell information transmission. It is possible that moderate cellular hypoxia retards the activity of oxygen-dependent enzymes involved in the synthesis of catecholamines (tyrosine and tryptophan hydroxylase) or acetylcholine (pyruvate dehydrogenase and choline acetyl transferase), but it cannot be excluded that the effect is on the release of transmitters, for example on the influx of Ca^{2+} or on Ca^{2+}-triggered presynaptic events. Whatever is the explanation, the demonstration of a free interval between the thresholds for electrical and membrane failure has provided the basis for the concept of the so-called "sleeping beauties", that is, neurones which are functionally inactive, but nonetheless viable.

Evidence exists that glycolysis is stimulated at degrees of cellular hypoxia which do not cause overt energy failure or other metabolic reactions which threaten cell viability. The main evidence derives from studies of mild to moderate hypoxia, a condition in which tissue lactate concentrations may increase to at least 10 μmol g^{-1} in the absence of measurable changes in high energy phosphates (Siesjo and Nilsson, 1971; Norberg and Siesjö, 1975) (fig. 5). Recently, measurements of extracellular pH (pH$_e$) during gradual reduction of cerebral blood flow have suggested that acidosis precedes the development of membrane failure, as this is reflected in release of K^+ from or influx of Ca^{2+} to cells (Astrup et al., 1977; Harris and Symon, 1984; Heuser, 1985). We may conclude, therefore, that glycolytic production of lactic acid is one of the first metabolic reactions to hypoxia and one that is not necessarily a threat to cell viability. We can only speculate on the molecular mechanisms involved, that is, on the existence of an appropriate oxygen sensor.

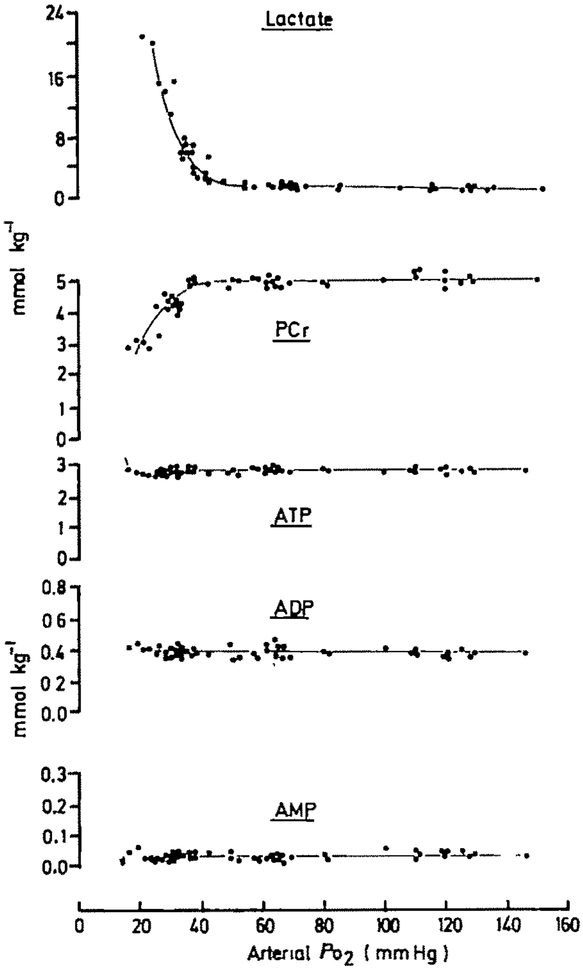

FIG 5 Influence of arterial hypoxia on labile phosphates and lactate content of cerebral cortex Note increase in lactate content at P_{O_2} values which do not perturb tissue concentrations of ATP, ADP, or AMP. (Data from Siesjo and Nilsson (1971).)

Although the evidence is indirect, we can conclude that energy depletion and accentuated anaerobic glycolysis occur first when flow has decreased to values at which the threshold of membrane failure has been transgressed. The most complete data exist for insulin-induced hypoglycaemia, during which depletion of high energy phosphate stores occurs *pari passu* with efflux of K^+/influx of Ca^{2+} (Harris et al., 1984; Wieloch et al., 1984). In fact, energy failure should be the event triggering dissipative ion fluxes. However, once this stage is reached, membrane failure can hasten and enhance the dissipation of tissue energy stores, contributing to the sudden collapse of cellular energy metabolism. One such accelerating event may be the increase in membrane permeability to ions, creating energy-wasting futile cycles. Another adverse event is the influx of Ca^{2+}, an ion which by itself may inhibit mitochondrial ATP production. Since acidosis has been shown to retard or even block mitochondrial respiratory reactions, pronounced lactic acidosis has a similar effect (see below). Once elicited, these reactions have a self-propagating nature.

Accepting that depolarization, dissipative ion fluxes, and energy depletion are coupled events, we must ask if they are prerequisites for other catabolic reactions. In all probability, the answer is yes. In graded hypoxia, lipolysis with accumulation of FFA does not occur until significant ATP depletion ensues (Gardiner et al., 1981) and in hypoglycaemia, gross FFA accumulation is observed first when K^+ efflux and ATP depletion are present (Wieloch et al., 1984). There are also theoretical reasons for assuming that lipolysis is triggered by ATP depletion and Ca^{2+} influx/release, and that the reactions triggered by loss of Ca^{2+} homeostasis encompass both protein phosphorylation and proteolysis. These reactions are further discussed below.

Potentially harmful reactions

The neurochemical events discussed are those that have been incriminated in the pathogenesis of ischaemic brain damage. In complete or near-complete ischaemia they are elicited in an avalanche manner. With gradual reduction of flow, there are two thresholds: one leading to mild to moderate lactic acidosis, and another with sudden metabolic failure, exaggerated lactic acidosis, massive release of neurotransmitters, loss of ion homeostasis, and catabolic reactions affecting both the lipid and protein constituents of cells. Evidence exists that potentially irreversible reactions are elicited first when ATP synthesis is reduced sufficiently to cause membrane failure and loss of ion homeostasis (Hass 1981; Siesjö, 1981; Meldrum, 1983; Siesjo and Wieloch, 1984a, b). As discussed below, many secondary reactions triggered by these initial events result from loss of Ca^{2+} homeostasis. However, although these events constitute a tentative scheme for the molecular pathology of ischaemic brain damage, they cannot account for all aspects. For example, it is now clear that, in an energy-depleted state, hyperglycaemia dramatically aggravates the damage incurred by ischaemia of a given density and duration (Myers, 1979; Rehncrona, Rosén and Siesjö, 1981; Siesjö, 1982, 1984a; Plum, 1983). (For an account of the effect of hypoglycaemia, see Diemer and Siemkowicz (1981).) Probably, this is because hyperglycaemia increases the pre-ischaemic tissue glucose concentration (complete ischaemia) or allows a continued supply of glucose to the ischaemic tissue ("trickle of flow"). Although the mechanisms have not been defined which mediate the effects of excessive acidosis, the possibility is discussed below that they encompass loss of volume regulation in glial cells, with ensuing oedema. For these reasons it seems reasonable to describe separately the series of neurochemical events which lead to neuronal damage and those causing astrocytic swelling with tissue oedema, indicating the roles played by deranged Ca^{2+} homeostasis and excessive acidosis.

NEUROCHEMICAL PATHOLOGY AT CELLULAR LEVEL

So far, we have discussed brain damage as an entity, without reference to the anatomical components of the brain, or its cell types. Clearly, the neurochemistry of ischaemic cell damage can only be approached in the knowledge that brain cells differ in their susceptibility to ischaemia. For example, it is necessary to explain not only why neurones are more susceptible than glial cells, particularly astrocytes, but also why neurones in certain anatomical locations are more prone to incur damage than others. A great number of brain insults affect neurones in so-called selectively vulnerable areas, for example the hippocampus, neocortex, cerebellum, thalamus and caudoputamen. However, within each of these areas, some cells are affected preferentially and selectively by ischaemia (Kirino, 1982; Pulsinelli, Brierley and Plum, 1982; Smith, Auer and Siesjö, 1984). In the neocortex these cells are the pyramidal cells in the middle cortical layers, in the hippocampus the pyramidal cells in layers CA1 and C3–4, in the caudoputamen the small or middle-sized pleomorphic neurones in the dorsolateral crescent facing the white matter, and in the cerebellum the Purkinje cells and to some extent also the basket cells. Two types of cells, the CA1 and CA4 pyramids of the hippocampus, show a perplexing sensitivity in that they incur irreversible damage after 2–5 min of ischaemia (Kirino and Sano, 1984; Smith, Auer and Siesjö, 1984).

At present, we lack a satisfactory explanation for these differences in vulnerability, but it seems clear that the explanation must be sought in the functional connections and neurochemical anatomy of the cells. At least one type of cell, the CA1 pyramidal cells in the gerbil, may develop morphological signs of death first after 3-4 days of recovery (Kirino, 1982), and display an increased rate of firing for at least 1 day after ischaemia (Suzuki et al., 1983). Circumstantial evidence exists that many of the selectively vulnerable cells have a high density of Ca^{2+} channels in their apical dendritic fields (Siesjö, 1981; Meldrum, 1983). In such cells, for example the CA1 and CA3 cells of the hippocampus, an important component of the excitatory drive is mediated by Ca^{2+} influx, this in turn being triggered by excitatory amino acids such as glutamate (Llinas, 1979; Heinemann and Pumain, 1980; Schwartzkroin and Wyler, 1980; Collins, Lothman and Olney, 1983). In fact, these cells have been considered to possess an innate tendency to epileptogenic firing which is curbed normally by an inhibitory tone conveyed by GABAergic neurones. In this context, it is important that analogues of glutamate, such as kainic acid, lethally damage neurones supposed to possess receptors for excitatory amino acids, by mechanisms which are assumed to involve uncontrolled influx of Ca^{2+} (Nadler, 1981; Coyle, 1983). Such cells are taken, therefore, as examples of neurones which may succumb by mechanisms related to Ca^{2+} toxicity, bearing in mind that the events discussed may in fact constitute more general phenomena.

Ca^{2+} homeostasis and Ca^{2+}-triggered events

Calcium serves as a messenger in key reactions in the cells and their membrane systems, regulating transmitter release, influencing membrane permeability, and modulating the activity of several enzyme systems (Carafoli and Crompton, 1978; Berridge, 1979; Borle, 1981). In some of these reactions, free Ca^{2+} is the reacting species but, in others, modulation is exerted by a Ca^{2+}–calmodulin complex (Greengard, 1979; Cohen, 1982; De Lorenzo, 1983). For all reactions, however, regulation/modulation requires that the free intracellular Ca^{2+} activity ($Ca^{2+}{}_i$) is maintained within a relatively narrow range, and certainly not outside the range 10^{-8}–10^{-6} mol litre^{-1}. This, in turn, requires regulation of $Ca^{2+}{}_i$ activity. The problem is that the $Ca^{2+}{}_e$ activity is approximately 1.5×10^{-3} mol litre^{-1} and that the membrane potential favours influx of Ca^{2+}. A first requirement, therefore, is that Ca^{2+} is constantly pumped out of the cell to balance the inward leak through specific or unspecific ion channels (fig. 6). Probably, one major mechanism achieving this is a membrane-bound Ca^{2+}–Na^+ exchanger ("antiport"), its energy source being the transmembrane Na^+ gradient created by the activity of Na^+–K^+-ATPase. Thus, when Ca^{2+} is carried in the outward direction it essentially "rides" on the Na^+ gradient. Since the Na^+ gradient between extra- and intracellular fluids (approximately 10 : 1) is not sufficient to maintain a Ca^{2+} gradient of the magnitude observed (about 10 000 : 1), one has to postulate an electrogenic process (carrying, for example 3–4 Na^+ for each Ca^{2+} ion), or the participation of ATP energy. Whatever is the mechanism, ATP depletion, membrane depolarization, and dissipation of the Na^+ gradient allow Ca^{2+} to enter the cell, with an ensuing increase in $Ca^{2+}{}_i$ activity.

Neuronal activity, especially when intense, causes constant influx of Ca^{2+}. Outward translocation of Ca^{2+} across the plasma membrane is probably too slow to allow fine regulation of $Ca^{2+}{}_i$ activity. Therefore, internal regulation requires that Ca^{2+} is transiently bound or sequestered. A major sequestration site is the mitochondria, which take up Ca^{2+} by an electrophoretic mechanism operated by the

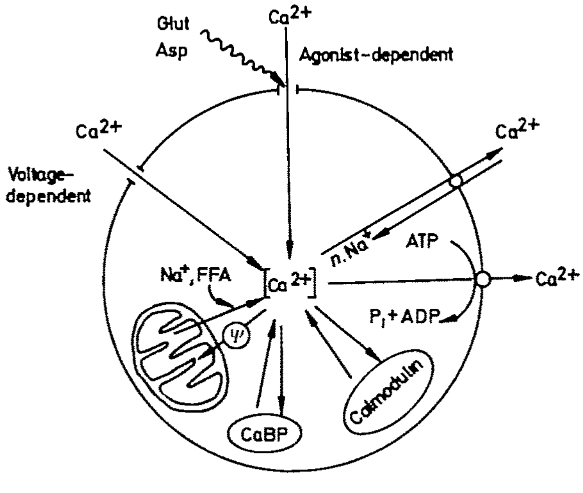

FIG 6. Schematic diagram illustrating principal features of intracellular Ca^{2+} regulation. Ca^{2+} is shown to enter by voltage- and agonist-dependent gates, and to be extruded by Ca^{2+}–Na^+ exchange, and also by ATP-driven transport. Binding to calmodulin and Ca^{2+}-binding protein (CaBP) is shown, as is sequestration by mitochondria via a voltage-dependent mechanism (ψ). Na^+ and FFA are assumed to enhance release of Ca^{2+} from mitochondria. (Modified after Berridge (1979).)

transmitochondrial potential gradient (the inside being negative)—a mechanism which takes preference over mitochondrial ATP production (Mela, 1977; Åkerman and Nicholls, 1983). However some Ca^{2+} is sequestered also in synaptic vesicles, and binding of Ca^{2+} occurs to phospholipids, and to proteins such as calmodulin and Ca^{2+}-binding protein (CaBP) (Baimbridge and Miller, 1982). The latter may have the function of shuttling Ca^{2+} to the plasma membrane, for subsequent re-export (Rasmussen and Weisman, 1983). All these mechanisms have a finite capacity and, when this is overloaded, Ca^{2+}_i increases.

Abnormal Ca^{2+}-triggered reactions of relevance to the present discussion include lipolysis, proteolysis, disassembly of microtubuli, and protein phosphorylation. These will be considered in turn.

Figure 7 illustrates, in schematic form, the turnover pathways of membrane-bound phospholipids, and the catabolic reactions elicited in an energy-depleted state. The cycle of reactions for the turnover of inosine phosphoglyceride (GPI) involves the breakdown of GPI to diphosphoglyceride (DG), and the energy-dependent reformation of GPI from DG. The second major pathway is that leading to breakdown of other phospholipid classes to lysophospholipids, the latter being reacylated at the expense of ATP. The two cycles are connected by a reversible pathway for base exchange. The direction of this reaction is highly dependent on CMP concentrations, that is on the energy charge of the tissue. In this general turnover of phospholipids, in itself probably reflecting modulation of the membrane matrix during synaptic activity, Ca^{2+} is involved in at least two ways. First, presynaptic Ca^{2+} influx triggers the release of transmitters, the interaction of which with membrane receptors increases the activity of phospholipase C, a Ca^{2+}-dependent enzyme. Second, Ca^{2+} is an activator of phospholipase A_2 (Wieloch and Siesjo, 1982).

Several factors tend to enhance phospholipid degradation during ischaemia: release of transmitters with accumulation of agonists at receptor sites, influx of Ca^{2+} with activation of phospholipase A_2, and increased concentrations of CMP produced by energy failure. These factors, and the cessation of resynthesis–reacylation, work in conjunction to release FFA. As shown in figure 7, some of the FFA accumulated must emanate from the operation of diglyceride lipases and lysophospholipases.

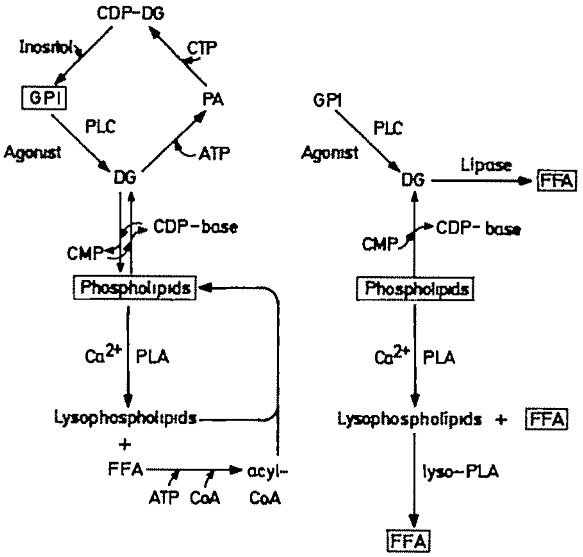

FIG 7. Diagram illustrating normal turnover of membrane-bound phospholipids (left panel) and pathways of lipolysis in an energy-depleted state. Degradation of inosine phosphoglyceride (GPI) to diglyceride (DG) is shown to occur by an agonist-activated and Ca^{2+}-dependent phospholipase C (PLC), and reconversion of DG to GPI via phosphatidic acid (PA) to occur at the expense of ATP and CTP. Degradation of other phospholipids, connected via a CMP-dependent base exchange mechanism to the GPI pool, is shown to occur by a Ca^{2+}-activated phospholipase A (PLA), the lysophospholipid formed then being reacylated at the expense of ATP energy. The right panel illustrates how energy failure causes accumulation of FFA, partly via the operation of DG lipase and lysophospholipase. (Slightly modified after Wieloch and Siesjo (1982).)

The second major effect of uncontrolled influx/release of Ca^{2+} is on the protein constituents of the cell. The cytoskeleton, the main components of which are neurofilaments and neurotubuli, are affected in two ways. First, by Ca^{2+} activation of neutral proteases, the neurofilaments can be degraded extensively (Schlaepfer, Zimmerman and Micko, 1981). Second, Ca^{2+} is involved in the depolymerization of neurotubuli which are polymerized from tubulin subunits in a process which requires the participation of a tau factor. Depolymerization is thought to occur by the formation of a complex between Ca^{2+}, calmodulin and the tau factor (Marcum et al., 1978; Kakiuchi and Sobue, 1981). The two effects thus elicited, (the degradation of neurofilaments and depolymerization of the neurotubuli), must seriously hamper processes which are dependent on an intact cytoskeleton, for example axopolasmic transport.

Other protein components affected by a deranged Ca^{2+} homeostasis are those forming parts of the receptor complex. The effects elicited include protein phosphorylation and proteolysis, and their importance resides in the fact they may produce long-term modulation of synaptic activity and membrane permeability. Phosphorylation of proteins by kinases probably underlies such phenomena as long-term potentiation and synaptic plasticity but, when pathologically enhanced, it may well cause aberrant synaptic activity which outlasts the ischaemic episode by hours or days (Browning et al., 1979; De Lorenzo, 1983; Rasmussen and Waisman, 1983). This phenomenon of hysteresis may occur both pre- and postsynaptically. At the presynaptic level, Ca^{2+}-induced phosphorylation of pyruvate dehydrogenase has been assumed to reduce mitochondrial sequestration of Ca^{2+} (Browning et al., 1979) and, postsynaptically, it may cause long-lasting changes in membrane permeability to ions. The former event could enhance release of transmitter for a given influx of Ca^{2+}, and the latter might accelerate dissipative ion fluxes triggered by agonist–receptor interaction, possibly also futile ion cycling with energy wasting (Siesjö and Wieloch, 1984a, b).

Yet another Ca^{2+}-triggered event, localized to postsynaptic membrane sites, may contribute to synaptic dysfunction. This is the proteolytic activity, which has been shown to increase the affinity of membranes from hippocampal tissue to glutamate, probably by uncovering of additional receptor sites (Baudry and Lynch, 1980; Lynch, Halpain and Baudry, 1982). Although much of the information on changes in synaptic activity triggered by Ca^{2+}, whether caused by protein phosphorylation or by proteolysis, is derived from experiments with repetitive stimulation or seizure activity, there are reasons to believe that they are also elicited by ischaemia (Yanagihara, 1980; Bodsch, Mies and Hossmann, 1983).

One may speculate, therefore, that Ca^{2+}-triggered pre- and postsynaptic events are the factors causing postischaemic hyperactivity and delayed neuronal death, as this has been demonstrated for the CA1 pyramidal cells in the hippocampus (see above).

Astrocytic swelling and brain oedema

Following brief ischaemic periods, especially in normoglycaemic animals, brain damage may occur as selective neuronal necrosis, and infarction with destruction of glial and vascular cells may be absent. However, even in these cases, ischaemia is accompanied by astrocytic swelling, often in perineuronal and perivascular positions. To a large extent, this cellular oedema results from translocation of water from extra- to intracellular spaces, and a net increase in tissue water content may be absent or small. In more prolonged ischaemia, and especially if hyperglycaemia is present, astrocytic swelling becomes pronounced and net oedema develops, often progressing during recirculation and resulting in tissue infarction. This process is also often what worsens the brain damage incurred following permanent occlusion of a cerebral artery, as in stroke. Two questions require answering in this context. First, what mechanisms lead to astrocytic swellings, and why do they not cause similar changes in neurones? Second, why is it that hyperglycaemia and excessive lactic acidosis accentuate oedema formation?

Cell volume regulation may be explained satisfactorily by the so called double-Donnan pump–leak hypothesis (Tostesson and Hoffman, 1960; MacKnight and Leaf, 1977). Any cell containing impermeable anions and possessing a membrane permeable to small ions such as Na^+ and Cl^- accumulates such permeable ions, with osmotically obliged water (Donnan system). However, a steady state with constant cell volume may be maintained if a normally permeable ion such as Na^+ is made effectively impermeable by being confined essentially to the extracellular compartment by active transport (double-Donnan system). This is assumed to be achieved by the operation of Na^+–K^+-ATPase, which maintains intracellular Na^+ low, and K^+ high. In this new situation, the actual cell volume is determined by the relation between the rate of Na^+ pumping and the rate of back leakage of Na^+ (pump–leak hypothesis). Clearly, any event which reduces the rate of Na^+ pumping or increases the rate of Na^+ influx, or both, causes the cell to swell.

Considerable information exists on cell volume regulation in erythrocytes which, at least in some species, can regulate their volume back to normal when exposed to hyper- and hypo-osmotic conditions (Cala, 1983). Two features of this regulation are of interest. First, cell swelling (in response to osmotic shrinkage) involves net gain of Na^+, Cl^-, and osmotically obliged water, while cell shrinkage (in response to osmotic swelling) involves net loss of K^+, Cl^-, and osmotically obliged water (fig. 8). Second, the ion fluxes occur as electrosilent Na^+–H^+, K^+–H^+, and Cl–HCO_3^- exchanges (antiport systems).

These ion and water fluxes may be useful paradigms for volume changes in brain cells during ischaemia. As a first approximation, one might assume that, if membrane permeability to K^+ increased, the cell would shrink (MacKnight and Leaf, 1977). Tentatively, this might explain why neurones show little evidence of swelling, or actually shrink, since influx of Ca^{2+} is known to increase markedly membrane permeability to K^+ (Meech, 1976). Realizing that this is a speculative deduction, we now turn our attention to glial cells, posing the question: why do they show a proclivity to swell? Considerable evidence exists that glial cell membranes contain Na^+–H^+ and Cl^-–HCO_3^- antiporters, and that conditions associated with increased K^+ values give rise to astrocytic oedema (Bourke, Waldman and Kimelberg, 1981; Kimelberg, Bourke and Stieg, 1982; Kimelberg and Bourke, 1984). Results from the same group indicate that the effect of K^+ is to release neurotransmitters, and that the swelling results from interaction of adenosine and noradrenaline with astrocytic membranes (Kimelberg and Bourke, 1984). One can tentatively assume, therefore, that such interactions increase Na^+ permeability in the sense that Na^+–H^+ exchange is enhanced, with coupled Cl^-–HCO_3^- exchange.

Figure 9 illustrates how the coupled ion fluxes may lead to cell swelling, and why acidosis can accentuate the process. In the upper part of the figure is shown an electrogenic Na^+-K^+ pump which translocates more Na^+ outwards than K^+ inwards. Such a pump would allow a negative ion such as Cl^- to follow the excess positive charge by electrophoretic drag. Essentially, therefore, the pump does not only act osmotically by keeping Na^+ in an extracellular position, but would actually expel Na^+, Cl^-, and osmotically obliged water. In the lower part are depicted the Na^+–H^+ and Cl^-–HCO_3^- antiporters, with emphasis that the source of H^+ and HCO_3^- is metabolically produced H_2CO_3. The Na^+–H^+ antiport seems to constitute a virtually universal means of extruding H^+ from cells, thereby regulating pH_i (Roos and Boron, 1981). Thus, the energy source created by the Na^+ pump is utilized, not only for export of Ca^{2+}, but also of H^+. However, if back leakage of H^+ into the cell occurs by export of HCO_3^- via the Cl–HCO_3^-

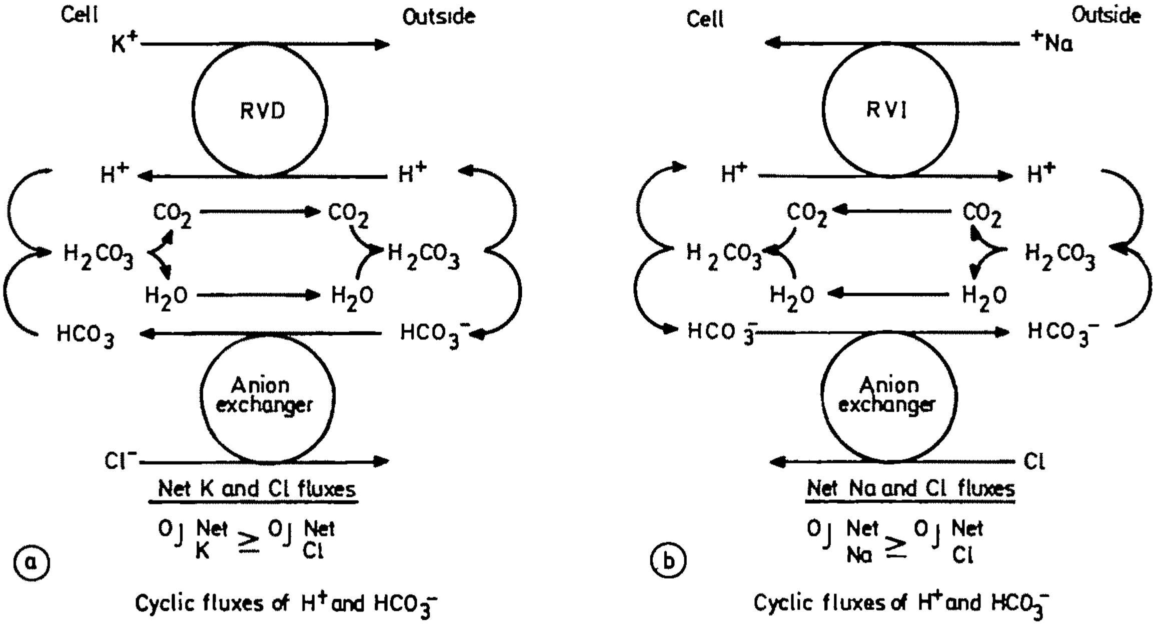

FIG. 8. Ionic fluxes associated with regulatory volume decrease (RVD) and regulatory volume increase (RVI) in erythrocytes challenged with osmotic swelling and shrinkage, respectively. The fluxes are shown to occur as electrosilent exchanges (K^+–H^+, Na^+–H^+, and Cl^-–HCO_3^-), with shrinkage during RVD involving loss of K^+ and Cl^- and swelling during RVI involving gain of Na^+ and Cl^-. Since fluxes of H^+ and HCO_3^- are cyclic, egress of K^+ and Cl^- leads to loss of H_2O, and uptake of Na^+ and Cl^- to gain of H_2O. (Reproduced with permission from Cala (1983).)

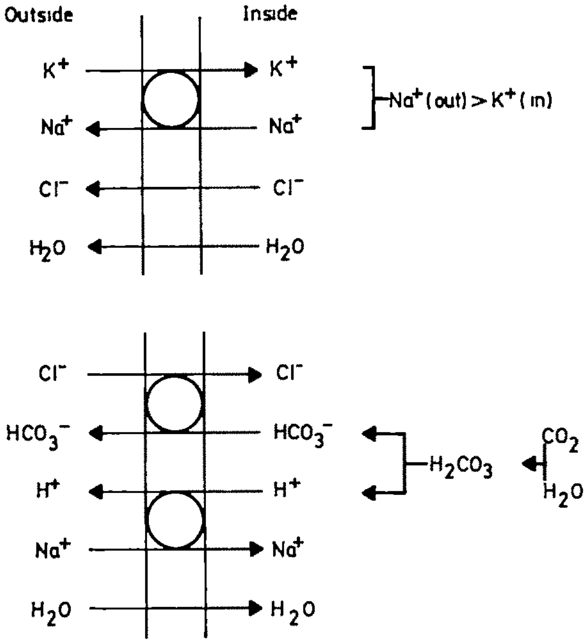

FIG 9. Ionic fluxes proposed to cause swelling of glial cells. The upper panel shows an electrogenic Na^+–K^+ pump which, by exporting positive charge, allows outward translocation of Cl^- and H_2O ("Na^+ pump"). The lower panel shows mechanism for uptake of Na^+ via Na^+–H^+ antiporter ("Na^+ leak"), with coupled Cl^-–HCO_3^- exchange, and flux of water from outside to inside. Swelling could occur by inhibition of the Na^+ pump or by stimulation of the Na^+ leak, or both, the second occurring as a result of agonist interaction with membrane and by intracellular acidosis (see text). (Slightly modified after Siesjo (1984a).)

exchanger, the sum effect of the antiporters is accumulation of Na^+, Cl^-, and water—that is, cell swelling. Possibly, this swelling tendency is normally counteracted by the electrogenic nature of the Na^+–K^+ pump (see above).

Given these facts, it is clear that acceleration of Na^+–H^+ exchange tends to cause cell swelling. Since astrocyte oedema accompanies not only ischaemia but also epileptic seizures and hypoglycaemia, it seems likely that the common mechanism is release of neurotransmitters, and "induction" of Na^+–H^+ exchange. However, the actual fluxes depend on the thermodynamic driving force which is the sum of the Na^+ and H^+ gradients. Thus, if H^+ increases within the cell, the exchange will be accelerated (Roos and Boron, 1981). Possibly, this is why acidosis accentuates astrocytic oedema and causes infarction.

Recovery events

Although the catabolic reactions occurring during ischaemia initiate cell destruction, the final cell damage is probably influenced by reactions elicited during recirculation. Such reactions may also be responsible for recruiting additional, irreversibly damaged cells in stroke, for example from the "penumbra" zone around the initial focus (Astrup, Siesjö and Symon, 1981; Astrup, 1982; Symon, 1985). The reactions encompass aberrations in protein metabolism, oxidative conversion of FFA accumulated during the ischaemia, and mitochondrial dysfunction.

It has been well documented that disaggregation of polyribosomes with accumulation of monosomes occurs when oxygen supply is restored (Cooper et al., 1977; Dienel et al., 1980); also that it may take hours to restore rates of protein synthesis, even following brief periods of ischaemia (Dienel et al., 1980; Bodsch, Mies and Hossmann, 1983). Interestingly, this delay is most pronounced in cell groups prone to incur damage, for example CA1 cells in the hippocampus. It is clear that events occurring during ischaemia (proteolysis, protein phosphorylation, disassembly of microtubuli) and during recirculation (disaggregation of polyribosomes, delay in recovery of protein synthesis) can retard or prevent recovery of neuronal function and metabolism. However, changes initiated during ischaemia, affecting protein components, may persist in the recovery period and cause sustained membrane dysfunction, the end result of which is cell death. Such reactions are those involving potentiation of synaptic efficacy from protein phosphorylation or proteolysis (see above).

Much attention has been focused on lipid changes in the post-ischaemic period, notably on the cascade of reactions elicited by the oxidative metabolism of arachidonic acid accumulated during the ischaemia. For example, it has been documented that prostaglandins, products of cyclo-oxygenase, accumulate in the period after ischaemia (Gaudet, Alam and Levine, 1980), together with at least one lipoxygenase product, 12-HETE (Wolfe, 1982). So far, 5-lipoxygenase products (leucotrienes) have not been identified in the brain. However, circumstantial evidence exists that free radical compounds are released. Some of these potentially harmful free radical species are formed during the enzymatically triggered arachidonic acid cascade, for example at the endoperoxide stage of the cyclo-oxygenase pathway (Samuelsson, 1979). Although several studies have failed to reveal that free radical damage occurs in ischaemia (Siesjö and Wieloch, 1984a, b), it may be that free radical damage occurs at sites so circumscribed that it cannot be assessed by analyses on tissue in bulk (Ginsberg et al., 1983). Circumstantial evidence that radical damage may occur are provided by the studies of Chan, Fishman and their co-workers on events elicited by administration of arachidonic and other polyunsaturated fatty acids to brain tissue *in vitro* and *in vivo*. These studies show that the pathophysiological effects elicited encompass cytotoxic (and vasogenic) oedema, inhibition of membrane-bound enzymes such as Na^+–K^+-ATPase, and reduced re-uptake of released neurotransmitters such as glutamate (Chan and Fishman, 1980; Chan, Kerlan and Fishman, 1983; Chan et al., 1983). The molecular bases of such effects are unknown, but one can speculate that FFA, or their oxidative conversion products, influence not only membrane structure and fluidity, thereby modulating enzymatic activities, but also increase membrane permeability to ions.

Finally, speculation exists on whether mitochondrial dysfunction persists or arises in the recirculation–reoxygenation period. During ischaemia, mitochondrial respiratory activity ceases and neither ATP formation nor Ca^{2+} accumulation can occur. In all probability, these functions fail even if the ischaemia is less than complete and some oxygen consumption persists. This is because acidosis inhibits mitochondrial respiratory functions (Hillered, Ernster and Siesjö, 1984) and because increased Na^+ and FFA contents enhance Ca^{2+} outflux from mitochondria (Harris, 1977; Crompton et al., 1978). Thus, even if some Ca^{2+} is translocated inwards, futile cycling could prevent net Ca^{2+} accumulation.

Clearly, recovery of energy metabolism following transient ischaemia requires that mitochondrial function is restored. Unless excessive acidosis occurs during ischaemia, mitochondrial respiratory activity, as assessed *in vitro* under optimal incubation conditions, is resumed even after 30 min of ischaemia. After 15 min of ischaemia, this occurs within the first 15–30 min of recirculation (Hillered, Siesjö and Arfors, 1984). In hyperglycaemic animals, though, such resumption is not observed after 30 min ischaemia, possibly because excessive acidosis causes permanent mitochondrial damage (Hillered, Ernster and Siesjo, 1984; Hillered, Siesjö and Arfors, 1984). It seems likely that if acidosis persists, for example during permanent MCA occlusion or from failure of adequate reflow, recovery of adequate mitochondrial function does not occur, and progressive tissue damage is incurred.

If recirculation causes resumption of ATP production and restoration of a normal pH, one would expect accumulation of Ca^{2+} in mitochondria. The results of Studer and Borle (1980) suggest that such accumulation may be enhanced by the alkalosis which develops during recirculation (Mabe, Blomqvist and Siesjö, 1983). Data derived from other tissues indicate that Ca^{2+} "overload" may be one mechanism of secondary mitochondrial function (Hearse, Humphrey and Bullock, 1978; Schanne et al., 1979). Under some circumstances, for example prolonged, incomplete ischaemia, total tissue Ca^{2+} content can increase appreciably (Yanigihara and McCall, 1982). It remains to be shown if this reflects sequestration into mitochondria, and if it constitutes a mechanism of mitochondrial damage (Meldrum, 1985).

ISCHAEMIC CELL DAMAGE· PROPHYLACTIC AND THERAPEUTIC MEASURES

Admittedly, present information on mechanisms of cell damage is incomplete and conclusions regarding the pathogenetic importance of the reactions discussed are based partly on circumstantial evidence. However, sufficient data exist to outline a series of reactions which serve the purpose of a working hypothesis, amenable to experimental testing. These reactions, which take on the characteristics of metabolic cascades, may be discussed conveniently on the basis of two schemes, one related to the effect of acidosis, and the other to Ca^{2+}-pathology. Each may be used as a tentative framework for characterization of pharmacological agents that may ameliorate ischaemic cell damage.

The reactions outlined in figure 10 suggest that the ATP depletion caused by ischaemia leads to two principal changes, both of which tend to enhance formation of oedema. One, the depolarization of nerve endings, has this effect by releasing transmitters that stimulate Na^+–H^+ (and Cl^-–HCO_3^-) exchange across astrocytic membranes, increasing the Na^+ "leak". The second principal change is the lactic acidosis which, by accelerating extrusion of H^+, has the same effect. In addition, increased H^+ activity interferes with mitochondrial respiratory activity, thereby reducing Na^+ pumping as well. Clearly, measures that retard lactic acid production, or increase intracellular pH could be beneficial by reducing oedema formation. It seems essential that hyperglycaemia is avoided in all cases with manifest

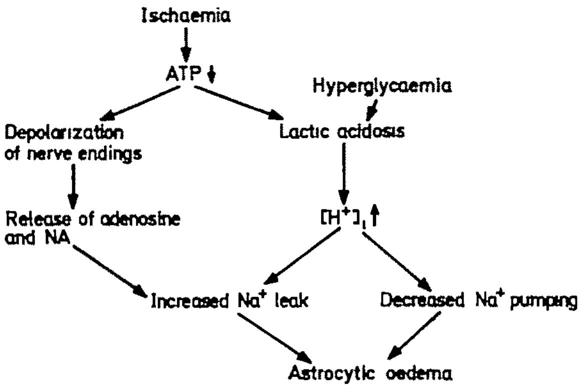

FIG 10. Scheme illustrating how energy failure causes glial swelling by inducing depolarization and release of membrane agonists, and by stimulating anaerobic glycolysis. For further details, see text (Reproduced with permission from Siesjo and Wieloch (1984b))

or suspected cerebral ischaemia, and that means of alleviating tissue acidosis are sought (Plum, 1983; Siesjö, 1984b). However, one can also envisage the therapeutic advantage of using pharmacological agents which reduce the activity of the Na^+–H^+ and Cl^-–HCO_3^- antiporters in the astrocytic membranes (Cragoe et al., 1982).

The second cascade of reactions is that leading to an aberrant protein and lipid metabolism, to membrane damage and receptor dysfunction and, ultimately, to cellular catabolism and cytoclasis (fig. 11). Key events in this cascade are the release of neurotransmitters, as a result of depolarization and presynaptic Ca^{2+} influx, and the activation by Ca^{2+} of lipases and proteases. One can foresee the therapeutic advantage of drugs that reduce pre- and postsynaptic Ca^{2+} influx, in addition to those that act on lipases and proteases. At present, interest in the use of Ca^{2+} entry blockers is focused mainly on the vascular effects of such drugs, but it seems justified to explore possible modulation of influx of Ca^{2+} into neurones, and its sequestration at intracellular sites. Likewise, continued efforts must be made to explore means of curbing the activity of lipases and proteases. Since ischaemia gives rise to long-term modulation of synaptic function, and causes secondary epileptogenesis, anti-epileptic drugs are potentially of considerable value. Finally, since we cannot exclude the possibility that some of the damage incurred by ischaemia may result from free radical mechanism, it may prove useful to administer antioxidants and free radical scavengers.

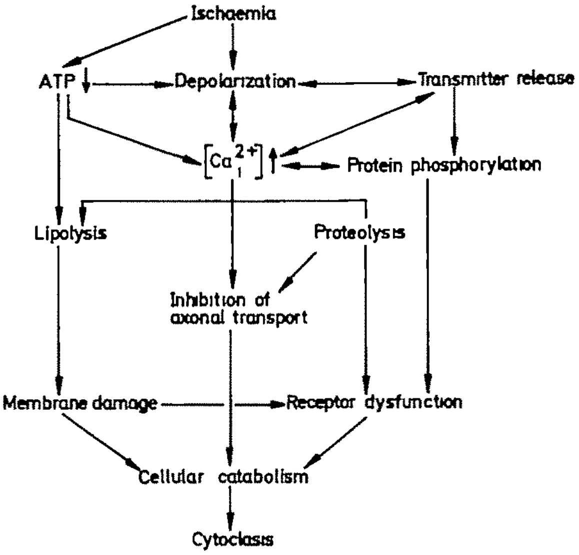

FIG 11. Schematic diagram illustrating cascade of reactions elicited by energy failure, depolarization, transmitter release, the accumulation of Ca^{2+} in the cytosol For further details, see text. (Slightly modified after Siesjo and Wieloch (1984a).)

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EEG MONITORING AND EVOKED POTENTIALS IN BRAIN ISCHAEMIA

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In 1875 Richard Caton observed electrical oscillations from the brains of animals which altered during dying and ceased with death. Similar alterations may follow cerebral circulatory arrest, exsanguination or inadequate cardiac action. The EEG fails within 20 s of cessation of the circulation and can recover within 30 s of its return, but there is a longer latency to return of EEG if ischaemia is more than momentary. The decline of the EEG was considered to be characterized by a decrease in the faster waves and an increase in the slower ones leading to electrical silence, with a reversal of this sequence during recovery (fig. 1). However, with abrupt onset of ischaemia rapid transition from a continuous "activated" EEG to a burst suppression pattern and silence is more often observed (Brierley et al., 1978). The EEG changes and their time course are comparable in both localized and global ischaemia, and similar but totally reversible depression is also found when brain metabolism is depressed by narcosis or profound hypothermia (Prior, 1973).

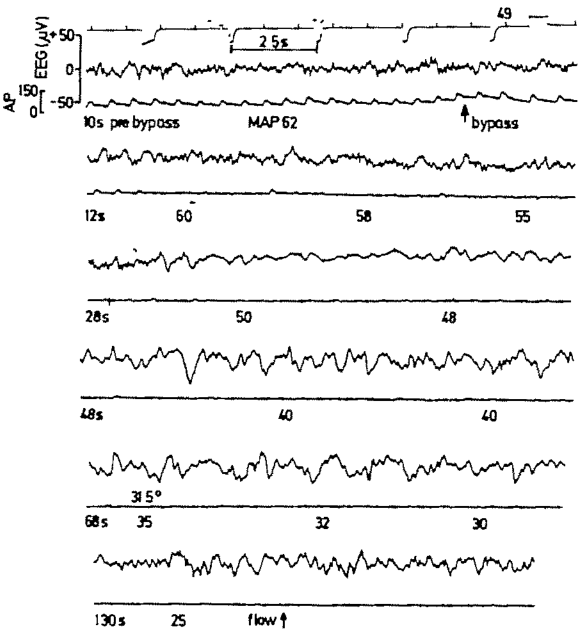

FIG 1. EEG alterations at onset of cardiopulmonary by-pass: simultaneous EEG and radial artery pressure (AP) recording in a 22-year-old woman undergoing pulmonary valvotomy and infundibular resection. Full flow 3.83 litre $\text{min}^{-1}\,\text{m}^{-2}$ increased to 4.70 litre $\text{min}^{-1}\,\text{m}^{-2}$ later. Biparietal electrode placement. Mean arterial pressures (mm Hg) indicated.

METABOLIC BASIS OF CEREBRAL ELECTRICAL ACTIVITY AND EFFECTS OF ISCHAEMIA

The EEG is a summation of volume-conducted potential fields from postsynaptic potentials of myriads of neurones, mainly of pyramidal type in the ganglionic layer 5 of the cerebral cortex. Neurones exhibit a resting potential difference of −70 mV across their membranes, maintained by ionic transport by the sodium–potassium pump. Propagation of impulses along axons is accomplished by depolarization (reduction) of the membrane potential, a threshold of −50 mV being sufficient to trigger the all-or-none action potential which reaches approximately +30 mV. Following chemical transmission across the synapses, postsynaptic potentials are triggered. These are of lower voltage than the action potential and are either excitatory (depolarizing) or inhibitory (hyperpolarizing). Simultaneous recordings from single neurones and of surface EEG demonstrate that trains of these underlying excitatory and inhibitory postsynaptic changes, rather than the action potentials, relate to the negative and positive waves of the EEG (Brazier, 1968; Eccles, 1968; Schmidt, 1978).

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Potentials evoked by sensory stimuli are transmitted from the receptor organs and along peripheral neural pathways to the appropriate area of cortex. There the primary response recorded by large electrodes is an integration of local postsynaptic potentials of a great number of cortical neurones. The substantial energy utilized, even in the resting state, by all these processes is derived from the phosphate bond of adenosine triphosphate (ATP) produced by oxidative metabolism of glucose by mitochondrial respiration. The ATP is used both for ion transport and synthesis of transmitter substances.

Cerebral circulatory insufficiency or arrest (whether from cardiovascular inadequacy or from impairment of cerebral perfusion by increased intracranial pressure) prevents delivery of adequate oxygen and glucose to the brain. Cerebral oxidative metabolism decreases, whilst the high energy compounds phosphocreatine and ATP are rapidly exhausted and not replenished. Anaerobic glycolysis is a poor source of ATP and leads to lactate production. ATP may then be insufficient to maintain neuronal resting potentials essential for integrated brain function and its by-product, the electrical activity recorded in the EEG. When cerebral metabolic demands are high, for example during hyperthermia or seizures, reduced energy supply is necessarily more likely to lead to ischaemic damage. With resuscitative measures, normal energy metabolism may be restored but, none the less, functional neurological deficit can be catastrophic—probably at least in part from damage to transmitters and deranged amino acid metabolism. Irreversible cellular lesions occur when the neuronal membranes and those of their internal organelles are damaged beyond repair, by whatever mechanism (Nilsson, Norberg and Siesjö, 1975; Siesjo, 1978; Raichle, 1983).

Thresholds for ischaemic depression of EEG and evoked potentials and for brain damage

Three ischaemic thresholds require consideration: onset of abnormalities in electrical activity, its extinction and irreversible cell damage. Whilst the first two (which can be recognized by non-invasive monitoring) are simply reflections of cerebral blood flow (CBF) and oxygen delivery in relation to metabolic needs (at least in the normal brain), the third adds a factor of time.

Cerebral blood flow thresholds for depression of electrical activity and for brain damage have been established with models of focal ischaemia, typically middle cerebral artery occlusion. Electrical abnormality occurs at regional cortical flow values of approximately 20 ml min^{-1}/100 g, followed by extinction of spontaneous EEG and evoked potentials at approximately 15 ml min^{-1}/100 g (Astrup et al., 1977; Morawetz et al., 1979). Single neurones show cessation of spontaneous electrical activity at a mean of 18 (range 6–22) ml min^{-1}/100 g. If flows of 14 ml min^{-1}/100 g or less persist for more than 45 min, their activity will not return with re-perfusion, and histology reveals selective neuronal necrosis (Heiss and Rosner, 1983). There is evidence that reversible neurological deficit occurs in the awake subject at slightly higher values—approximately 23 ml min^{-1}/100 g (Jones et al., 1981) and that evoked potentials persist to slightly smaller values of CBF than spontaneous EEG (Shapiro, 1978). Permanent neurological deficit and infarction in the middle cerebral artery territory are described when flows of 12 ml min^{-1}/100 g are sustained for 2–3 h (Jones et al., 1981), massive release of K$^+$ ions being observed with flows in the region of 6 ml min^{-1}/100 g (Astrup et al., 1977).

With global brain ischaemia, additional factors require consideration. Autoregulation of CBF usually fails at values of mean arterial pressure (MAP) less than 60–70 mm Hg (Lassen, 1959) and then CBF is pressure passive. In hypertensive animals autoregulation fails at higher pressures (Fitch et al., 1978). The lower limit for autoregulation may be as high as 113 ± 17 mm Hg in hypertensive patients with resting MAP within the range 145 ± 17mm Hg; however, with prolonged effective antihypertensive treatment, there is some evidence of readaptation towards normal (Strandgaard et al., 1973; Strandgaard, 1976). An added complication is that, in damaged brains, the usual interrelationships between CBF, metabolism and electrical activity may not obtain (Paulson and Sharbrough, 1974).

Thresholds for brain damage following global ischaemia are defined by a critical combination of reduced blood flow leading to electrical silence and time. Thus, in the Rhesus monkey, acute profound arterial hypotension had to be sustained for at least 15 min with cerebral perfusion pressures (CPP) of less than 25 mm Hg and EEG and evoked potential silence, to produce even restricted damage (Brierley et al., 1969; Meldrum and Brierley, 1969). Longer periods led to more extensive ischaemic necrosis. With less abrupt but progressive hypotension induced over 2–3 h in the cat, CBF became pressure-dependent at MAP values less than approximately

65 mm Hg and electrical abnormalities began at 30–40 mm Hg, with EEG and evoked potential silence occurring between 10 and 30 mm Hg. Infarction occurred when MAP was held at 25 mm Hg (and in one instance at 35 mm Hg), with comparable reduction in CBF to 8–11 ml min^{-1}/100 g, for 20 min (Graham et al., 1979; Gregory et al., 1979; Mackenzie et al., 1979).

It is difficult to compare the many models of brain ischaemia because of widely differing methods and rates of producing ischaemia (some without parallel in clinical experience in man). Species differences are evident, partly from variations in cerebral vascular anatomy and physiology. Variations in normal ranges for MAP, different depths of anaesthesia, use of artificial ventilation and muscle relaxants, in addition to widely variable definitions of "recovery" also prejudice comparisons. Moreover, in almost every study reported, there are wide individual variations in CBF and CPP values for onset of electrical abnormalities and for infarction, even though mean values show consistent trends.

Distribution and electrical correlates of ischaemic brain damage

The end result of ischaemic stress to neurones is an alteration in cellular morphology, "ischaemic cell change", which evolves over several hours. Complete circulatory arrest produces selective necrosis of vulnerable neurones in a characteristic distribution within the brain (Brierley, 1976). The widespread electrical abnormalities and their evolution allow prediction of the severity of brain damage (Lindgren, Petersen and Zwetnow, 1968; Brierley et al., 1971; Prior, 1973). When there is a rapid and considerable reduction in cerebral perfusion pressure, but not total cerebral circulatory arrest, ischaemic brain damage occurs along the boundary zones between the territories of the main cerebral arteries (Adams et al., 1966; Brierley et al., 1969). This pattern of damage is common to a wide variety of clinical conditions, including profound arterial hypotension and increased intracranial pressure (Graham, 1977). The earliest EEG alterations are found in the boundary zones, before the cortex in the middle of the artery territory is affected. The extent of the infarction is proportional to the severity and duration of the EEG depression during the insult and the early recovery period (Brierley et al., 1980; Malone, Prior and Scholtz, 1981).

The arterial boundary zone distribution of brain damage and of the earliest electrical abnormalities suggests that these are the optimal sites for monitoring electrodes in global ischaemia. In contrast, electrodes should be placed over the main artery territory at risk when carotid artery or an intracranial artery occlusion reduces flow locally and collateral circulation is insufficient. If the ischaemic stress is primarily subcortical, the use of somatosensory evoked potentials rather than EEG monitoring should be considered (Hume and Cant, 1978; Symon et al., 1979).

METHODS FOR WARNING OF BRAIN ISCHAEMIA

Prevention of brain ischaemia depends upon reliable evidence of its imminence. Prevention of permanent ischaemic brain damage depends upon taking corrective action immediately warning signs appear. In man, ischaemia and brain damage occur at thresholds that vary between different individuals and clinical circumstances (table I). They are often multifactorial, even if not overtly so. Thus, ischaemia may lead to fits and a higher cerebral metabolic demand for oxygen but poorer oxygen delivery, all combining to increase damage. A critical combination of adverse factors may be unexpected and unrecognized in an individual unconscious patient. Some factors such as extra- or intracranial vascular disease, impaired autoregulatory capacity and cerebral metabolic requirements at a given temperature or anaesthetic depth, may not even be known. Routine clinical monitoring of ECG, arterial pressure and blood-gas tensions only indicates the adequacy of factors supporting brain function. The EEG and evoked potentials are more valuable because they can monitor continuously the end result at a neuronal functional level. If taken in the context of the supportive factors, contributory causes of ischaemic depression can be identified and the effect of appropriate treatment monitored.

EEG and evoked potential recording

The general principles for neurophysiological recording are detailed in a number of standard works. For EEG methodology, Tyner, Knott and Mayor (1983), Cooper, Osselton and Shaw (1980) and Binnie, Rowan and Gutter (1982), taken sequentially, address readers of progressively increasing sophistication. For evoked potential recording, Chiappa (1983) and Halliday (1983) provide superbly clear and comprehensive accounts of methodology and applications.

Neurophysiological monitoring requires impeccable electrode contact with the patient and avoidance of interference from unwanted signals. Specific methods for recording EEG and evoked potentials in the operating theatre and the intensive care unit have been described elsewhere (Prior, 1973, 1979; Greenberg, Mayer et al., 1977; Greenberg, Becker et al., 1977; Hume and Cant, 1978; Raudzens, 1982; Goff et al., 1983; Grundy, 1983). Success depends upon attention to a number of practical points:

(1) *Choose the best electrodes.* Sterile intradermal needle EEG electrodes made of platinum-iridium alloy are used for quick access with least disturbance to the patient. For longer recordings silver–silver chloride EEG disc electrodes fixed to the scalp with collodion and filled with conductive jelly are required. Leads should be fixed securely with both. For recording at craniotomy, special electrodes are made usually of fine wires carried in light-weight plastic sheeting.

(2) *Measure the electrode contact impedance* and monitor it throughout if possible. It should be less than 5 and usually 1–2 kΩ; if higher there will be more interference.

(3) *Use appropriate recording and reference electrode sites.* For EEG, bilateral fronto–centro–parietal or bi-parietal derivations cover the middle cerebral artery territories and the main arterial boundary zones, whilst avoiding sources of unwanted signals such as eye or jaw movements. When applying electrodes to the back of the head or neck, avoid undue neck flexion which can increase intracranial pressure by venous obstruction.

(4) *Record from more than one area if possible.* It is important to balance the need for simplicity against that for adequate information. Whilst a bi-parietal derivation may be quite adequate for general surveillance, warning of focal ischaemia would be provided better by appropriate regional placement of recording electrodes to enable comparison with contralateral homologous areas. Spare electrodes, placed before surgery, allow for unobtrusive substitution in the event of faults developing.

(5) *Have the pre-amplifiers near to the patient's head.* Transmitting amplified signals rather than those of a few microvolts, reduces the effect of interference.

(6) *Ensure patient safety.* Take account of modern recommendations and make regular safety checks. Conventional isolation amplifiers, opto-kinetic couplers or infra-red technology separate the patient from dangerous voltages. Avoid multiple mains leads or multiple earths and ensure that apparatus is safe during surgical diathermy or defibrillation.

(7) *Use special filters or circuits to minimize interference.* These include input isolation, notched filters set at mains frequency (50 or 60 Hz) and radio frequency traps which may allow continuous recording to continue during surgical diathermy (Van der Weide and Pronk, 1979) or to be cut out to avoid blocking or damage to the apparatus. Equipment for evoked potential averaging normally incorporates rejection systems (e.g. on the principle of Schmitt triggers) which prevent acceptance of high voltage potentials which are likely to be artefactual.

(8) *Obtain sufficient baseline or normative data* before the time of risk so that effects of anaesthesia, sedation or hypothermia can be assessed. This may also imply monitoring the EEG during recordings of cerebral evoked potentials so that any depression from anaesthesia is not mistaken for ischaemia. If techniques are standardized as much as possible, unusual features or abnormalities will be noticed more easily. Technicians must have adequate training and equipment to be capable of flexibility.

(9) *Do not treat neurophysiological data in isolation.* Most alterations are non-specific and can only be interpreted sensibly in context. Polygraphic recording of EEG with other physiological variables on a single well annotated chart, avoids many ambiguities.

(10) *Use appropriate processing and displays to reduce and clarify the data.* Special methods are virtually obligatory for long periods of EEG monitoring, because of the complexity and bulk of the traditional multichannel chart recordings and the inherent difficulties in recognizing trends and providing quantification.

EEG analysis and display

The EEG can be described or quantified by various methods (Handbook 1972, 1973; Rémond, 1977). The inherent tendency of slow waves to be of higher amplitude than faster ones (figs 1 and 2) requires that EEG monitoring systems may need compensatory pre-filtering. Data reduction then takes one or both of two general forms: (1) continuous measurement of amplitude by integration or amplitude variability envelope. These are designated time domain analyses, in that the chosen variable is plotted against time, for example as in the cerebral function monitor (CFM) (Maynard, Prior and Scott, 1969) (fig. 2). (2) Frequency analysis, usually as an average over seconds or even minutes and derived from tuned filters or fast Fourier and related transforms. These are designated frequency domain analyses, in that a chosen measure such as EEG power is plotted against frequency. Wave period analysis and baseline (zero) crossing counts, although essentially time domain methods, are often displayed to give a pseudo-frequency domain effect. In general, being based on averages over chosen epochs of time, frequency domain analysis has inherent disadvantages for monitoring. It assumes that the EEG is stationary, it masks events that are short-lived or atypical with respect to the whole epoch, and it cannot indicate the variability of the signal, except from sequential or overlapped epochs.

Displays of processed EEG take many forms. The simplest are the single line representing continuously integrated or envelopes of amplitude. Frequency data may be reduced to a mean (which can lead to ambiguity and conceal significant events such as burst suppression activity or near electrical silence) or displayed as ratios (equally risky) or as detailed power spectra by a series of histograms. Smoothing and sequential presentation result in the compressed spectral array (CSA) (Bickford et al., 1973) or grey scale dot formation density modulated array (DSA) (Fleming and Smith, 1979). The new generation of monitors display combined time and frequency domain data such as wave period and amplitude (Klein and Davis, 1981), CSA with integrated amplitude (Myers, Stockard and Saidman, 1977; Pronk, 1982) or the modified CFM (CFAM) (Maynard, 1977; Maynard and Jenkinson, 1984) (fig. 3).

Critical comparisons of various monitoring methods regarding their performance in detecting ischaemia change are few and often disappointingly inadequate. Several aspects have to be considered, such as efficiency in demonstrating relevant abnormality, ability to respond quickly to ischaemic change but not excessively to fluctuations in level of consciousness or with artefactual interference (Matoušek, Arvidsson and Friberg, 1978). In focal ischaemia, CBF has been correlated with mean EEG frequency quantified by various methods (Tolonen and Sulg, 1981). In patients undergoing carotid endarterectomy, Chiappa, Burke and Young (1979) found that analysis by minicomputer (CSA combined with integrated amplitude from each hemisphere plus asymmetry detection) invariably rendered the EEG change more apparent than did conventional recording. Significantly, these authors noted that their 4-s CSA epoch so "smoothed" the trace that the burst-suppression pattern from fast-acting barbiturates was not evident, an observation also noted by Levy (1984) in cardiac surgery. Further, the only EEG parameter significantly associated with damage after operation was amplitude depression.

There have been two extensive comparative studies for intraoperative monitoring during possible global ischaemia. In cardiac surgery, Pronk (1982) and Pronk and Simons (1982) found that each of the five major types of analysis tested in 30 partients was very effective, but they concluded that a combined frequency (zero cross) and amplitude (integration) display gave greatest safety. They indi-

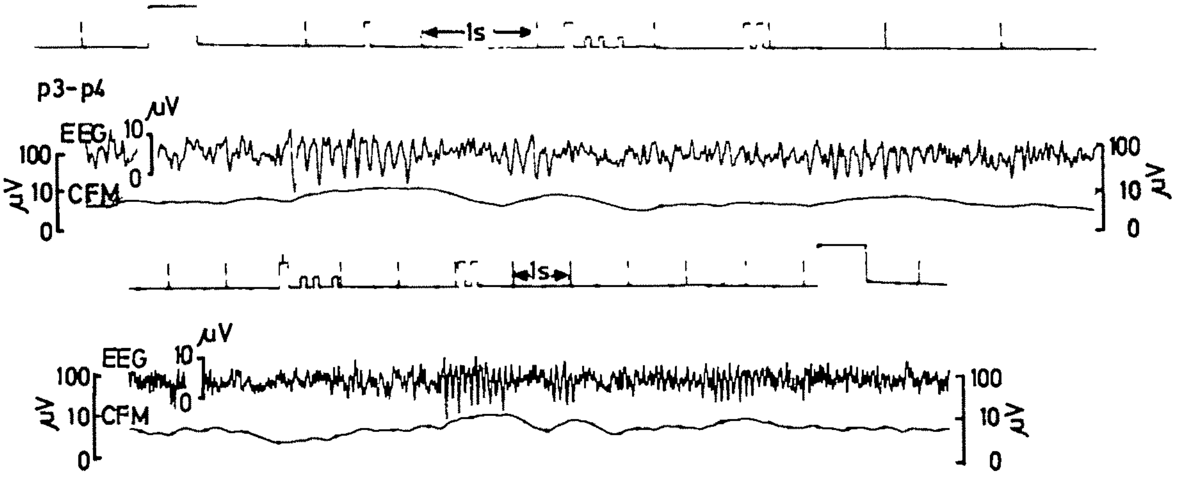

FIG 2. Simultaneous recording of EEG and cerebral function monitor (CFM) from left and right parietal electrodes in a normal subject, awake with the eyes closed. The same data are presented at two different chart speeds to show how the increased peak-to-peak amplitude (μV) of a burst of alpha waves results in an increase in amplitude of the CFM trace. CFM amplitude fluctuates with the amplitude envelope of the raw EEG.

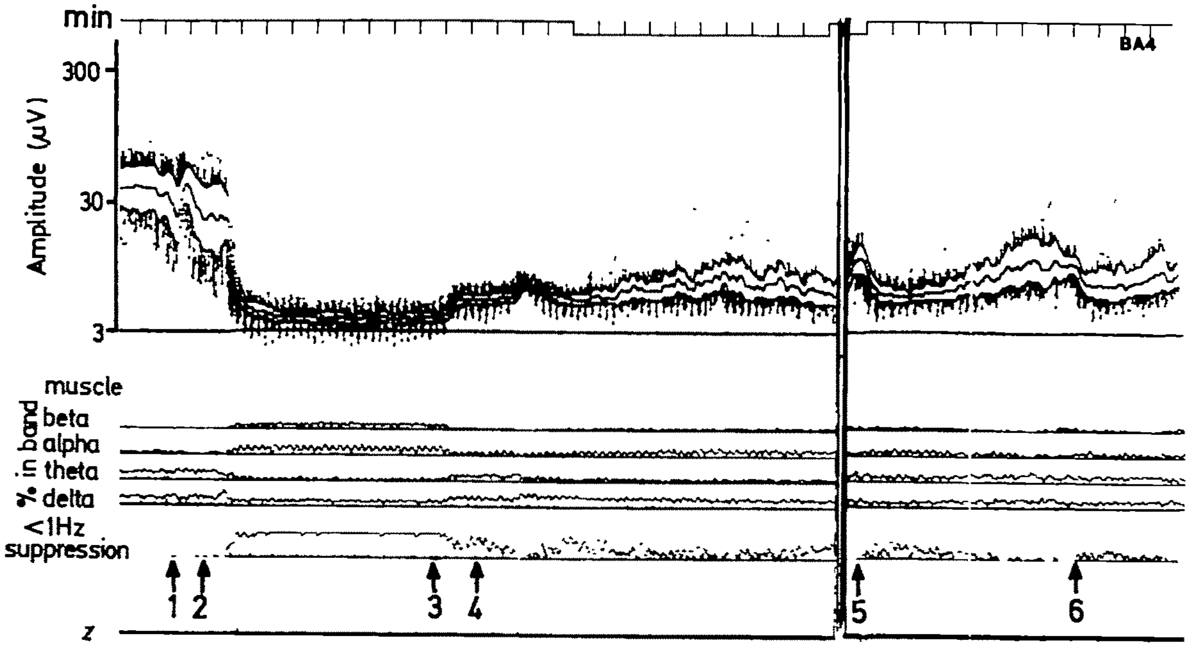

FIG 3. CFAM recording during combined hypoxia and ischaemia: the CFAM has a passband of 1–27 Hz and a fully logarithmic scale. Amplitude (calibrated peak-to-peak at 10 Hz) is given as backwards weighted mean values updated every 2 s for mean voltage, 90th and 10th centile values and peaks and troughs exceeding these. Frequency analysis is given as the percentage of power falling into the traditional EEG frequency bands (beta, alpha, theta, delta) and also activity of less than 1 Hz and periods of suppression below a preset voltage limit. Muscle potentials and electrode impedance (*z*) can also be indicated. This recording is from left centro-parietal extradural electrodes in a spontaneously breathing baboon anaesthetized with Althesin infusion 0.42 ml kg^{-1} h^{-1}, Pa_{O_2} 3.99 kPa and right common carotid occlusion (Brierley et al., 1980). At (1) left common carotid occlusion, mean arterial pressure (MAP) increased from 131 to 163 mm Hg, (2) trimetaphan 38 μg, MAP decreased to 48 mm Hg and vertebral Doppler pulse became undetectable, (3) carotid clasps removed and (4) metaraminol restores MAP to 143 mm Hg and Doppler pulse returns. Subsequent myoclonic jerks and opisthotonic spasms controlled by additional bolus doses of Althesin 0.2 ml at (5) and (6).

cated that choice of methods could reasonably be made on grounds of cost and simplicity, factors also discussed by Levy and others (1980). Comparisons are also available between 28 spectral EEG parameters and 14 CFAM measures (fig. 3) from 33 patients during controlled hypotension or cardiopulmonary bypass (Matoušek et al., 1985). Most significant alterations with onset of ischaemic stress concerned amplitude rather than frequency content. Features most highly correlated with decreasing arterial pressure were mean amplitude from the CFM or CFAM and amplitudes of delta, upper alpha and lower beta bands or summed amplitudes from spectral analysis. However, frequent disturbance of the delta band by artefact during surgery entails that amplitude in the 10–17 Hz range is of greater interest for monitoring, and it can be derived from simple analog filtering. This also allows clear display of burst-suppression activity or electrical silence. The multimodal character of EEG changes at onset of bypass has been emphasized by Levy (1984), who demonstrated in 30 patients that neither mean frequency nor spectral edge frequency reflected their complexity, and he concluded that univariate descriptors were inadequate for monitoring the EEG changes in a large percentage of patients.

Specification for EEG monitoring systems

It is evident from these reports that many EEG measures are sensitive to changes induced by ischaemia and practical differences between monitors relate much more to cost, susceptibility to artefact, ease of use and of measurement, and interpretation of displays. Interestingly, no study appears to have addressed the psychology of communicating information by such monitors in operating theatres and intensive care units. Monitors should be powerful in separating different, in addition to classifying similar, EEG patterns, be easy to interpret in clinical and EEG terms, be theoretically well founded, numerically stable, and robust even in the presence of small deviations from the model on which the analysis method is based (Matthis, Scheffner and Benninger, 1981). Operation should be automatic without need for gain adjustments; signals likely to be artefactual should be rejected automatically. Clear time-coding and warnings of high electrode impedance and interference should be given. In order to detect ischaemia, low voltage activity must be emphasized: conditions where cerebral metabolic demands are high, such as seizure discharges or responses to pain, must also be recognizable. Time domain (e.g. period-amplitude) analyses are well suited to the purpose, generally easy to learn to read and, if filters exclude slow waves, are not affected by artefacts. They are less disturbed by changing depth of anaesthesia than frequency ratios and more informative than mean values. Modern monitors will provide a combination of amplitude and frequency distribution information to give early warning of brain ischaemia. Ideally, these features should be in a compact apparatus which also has facilities for display of other physiological variables and evoked potentials.

Evoked potential analysis and display

When a sensory stimulus occurs, potentials are elicited at the receptor site and then travel via neural pathways to the appropriate central relay nuclei and primary cortical representation areas. The evoked spinal, brainstem and cerebral potentials individually are of relatively low voltage and may well be unrecognizable amongst other concurrent higher amplitude activity. However, averaging sequentially from the time of each of a train of stimuli enhances any time-locked potentials ("signals") at the expense of unrelated "noise". Small averaging computers are used to control stimulus delivery and process and display the averaged sensory evoked potentials. Appropriate evoked potentials (fig. 4) in patients at risk of brain ischaemia include *brainstem auditory evoked potentials (BAEP),* a series of five waves occurring within about 6 ms of a sound. The latency difference between the first and fifth waves indicates transmission time through auditory nerve and brainstem. *Somatosensory evoked potentials (SSEP),* from electrical stimulation of peripheral nerves, can be recorded over spinal cord and at somatosensory cerebral cortex about 20 ms after stimulation at the wrist (Mauguière, Desmedt and Courjon, 1983). The difference in latency between cortical and upper cervical spine potentials, designated the central somato-sensory conduction time (CCT) (Hume and Cant, 1978) is about 5 ms. *Visual evoked potentials (VEP)* to flash stimulation have some place in the detection of ischaemia, but those to pattern reversal are generally inappropriate in sedated or anaesthetized subjects. For warning of ischaemia during surgery or intensive care, recording of peripheral potential to confirm entry of the

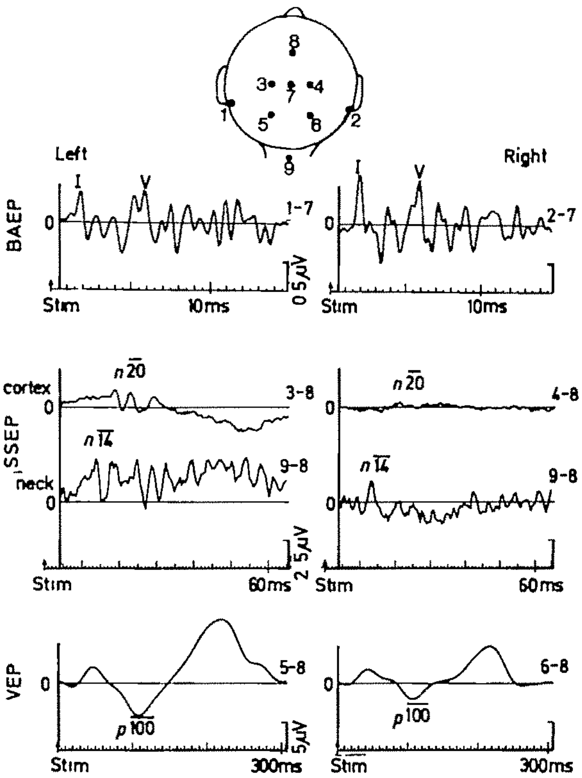

FIG 4. Averaged sensory evoked potentials in traumatic coma: in a 24-year-old man 4 days after head injury with extensive cranial fracture on the right and underlying contusion. Fixed dilated pupils and no response to pain on admission; flexion of right limbs to pain after surgical debridement of the wound. Auditory brainstem potentials (BAEP), somatosensory potentials over 2nd cervical vertebra and contralateral somatosensory cortex following median nerve stimulation at the wrist (SSEP) and visual evoked potentials to binocular flash stimulation (VEP). Note slight delay of BAEP wave I on the right, but otherwise normal brainstem auditory potentials, depressed cortical SSEP and reduced amplitude VEP over the right hemisphere. Six weeks later, the patient was conscious and active with a left hemiparesis but no overt visual field defect; he was being transferred to a rehabilitation unit.

stimulus is an essential prerequisite to interpretation of abnormal cortical potentials.

Display and analysis of evoked potentials for ischaemia detection or serial assessment must permit simple quantification. Ischaemia affects amplitude more than latency with abolition of potentials when CBF is less than approximately 15 ml min^{-1}/100 g. Focal ischaemia may produce significant amplitude asymmetry, but an amplitude ratio of 2 : 3 can be normal in cortical potentials in unanaesthetized subjects (Halliday, 1983). Greenberg, Mayer and others (1977), Lindsay and others (1981), Rappaport, Hall and others (1981) and Rappaport, Hopkins and others (1981) have used measures such as presence, number, complexity and symmetry of waves in the evoked potential as an index of preservation of function. This is useful for cortical potentials but unfortunately sedation, anaesthesia and hypothermia readily depress all but their primary components. In contrast, the more robust BAEP and CCT latencies are unaffected; they reflect subcortical functions and are more amenable to simple measurement.

THRESHOLDS FOR ISCHAEMIA AND BRAIN DAMAGE IN MAN

Although experimental observations have provided valuable fundamental understanding of ischaemic brain damage, it is oversimplistic to extrapolate from them to clinical practice. In man, arterial hypertension and occlusive vascular disease in extracranial portions of the cerebral arteries are common compared with experimental animals. Many accidental insults are complex, with, for example, mixed hypoxia and ischaemia or combinations of local brain injuries, impairment of autoregulation and adverse systemic factors. Average "safe" values for cerebral perfusion may not necessarily apply to any one individual. The variations in CPP thresholds for electrical abnormality and extinction in different clinical circumstances are wide (table I) and are now illustrated by clinical examples.

Controlled hypotension

Since the introduction of this technique to produce a bloodless field during surgical anaesthesia, there have been anxieties regarding the effects on perfusion of brain and other organs (Review, 1975; Heuser, McDowall and Hempel, 1984). Although there are many experimental data, only a few investigators have mentioned thresholds, usually MAP of 20–40 mm Hg, for EEG deterioration or failure in man. This is probably partly because of inherent dif-

TABLE I. *Mean thresholds for ischaemia-induced* EEG *or sensory evoked potential abnormality for various species and types of stress.* † *Not stated*

	Cerebral perfusion pressure or mean arterial pressure* (mm Hg)		
Model	Control	Onset EEG or SEP abnormality	EEG or SEP silence
Profound hypotension			
(TMP) *M. mulatta*	†	30	25
Brierley and others (1969)			
Hypoxic hypoxia (P_{aO_2}<20 mm Hg)			
P. anubis	118 ± 19	106 ± 27	96 ± 27
M. mulatta	101 ± 15	81 ± 24	55 ± 34
Brierley and others (1980)			
Cardiac surgery*			
Onset bypass	79 ± 13	44 ± 12	15
Later decreases	81 ± 15	24 ± 10	21 ± 4
Prior and others (in preparation)			
Controlled hypotension*			
SNP	69 ± 16	61 ± 10	—
TMP	69 ± 12	54 ± 8	—
Thomas and others (1985)			
Traumatic coma	54–60	31 ± 13	24 ± 12
Prior and others (1982)			

ficulties in EEG quantification. Patel (1981) used the CFM, a monitor that had provided simple quantification in other circumstances. He was able to show in 45 healthy patients that the degree of depression of the monitored EEG was related to the rate of decrease of arterial pressure induced by a combination of ganglion and beta blockade with head-up tilt. EEG changes were minor unless pressure was reduced rapidly and was less than a systolic value of 60 mm Hg. Thomas and colleagues (1985) demonstrated that every patient in a group of 20 studied during routine surgical procedures, showed a decrease in EEG amplitude (measured by the CFM and by Fourier analysis) as MAP was reduced electively by sodium nitroprusside (SNP) or trimetaphan (TMP). The amplitude decline began once MAP decreased below a mean threshold of 57±9 mm Hg (table I). In almost half the patients there was a highly significant correlation between simultaneous 10-s measurements of MAP and average CFM voltage whilst MAP was decreasing. In no instance was there any suggestion of neurological sequelae. The degree of EEG depression was significantly greater below MAP 50 mm Hg with TMP than SNP (fig. 5), confirming the experimental findings of Ishikawa and McDowall (1981), whose study is particularly important. A clear relationship was demonstrated between CBF and EEG "power" measured by the average voltage of the CFM trace during hypotension and both were significantly better sustained by SNP than TMP at equivalent low values of arterial pressure.

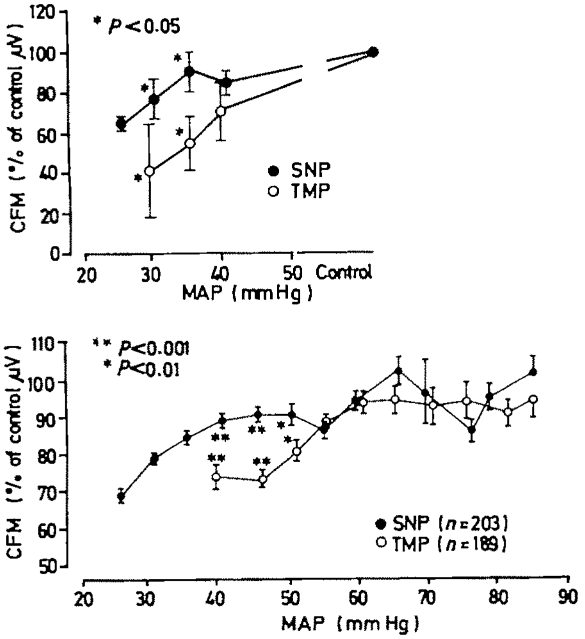

FIG 5. Controlled hypotension, comparison of sodium nitroprusside (SNP) and trimetaphan (TMP) in cat (Ishikawa and McDowall, 1981) and man (Thomas et al., 1985). Mean CFM voltages as percentage of control for grouped data from 10 animals and 20 patients. (Redrawn from above with permission of authors and publisher.)

Experimental and clinical observations in controlled hypotension reveal wide inter-individual differences in cerebral effects of ischaemia such as the thresholds for alterations in CBF, EEG and evoked potentials. They are not entirely predictable on the basis of age, previous MAP or method and rate of pressure reduction. Nonetheless, there appears little evidence that major depression of CBF or electrical activity occurs at MAP greater than 60 mm Hg in normotensive patients who are presumed capable of autoregulation. Furthermore, there may be little benefit, in terms of reducing blood loss, in decreasing pressure to less than this value (Donald, 1982). If greater hypotension is necessary, for example in neurosurgery, presently available evidence suggests slow induction by SNP rather than TMP, under EEG or evoked potential control, to minimize the risks of ischaemic brain damage (McDowall, 1985).

Cardiac surgery with cardiopulmonary bypass

Reduction in arterial pressure is one of many factors that may disturb the brain at the onset of cardiopulmonary bypass and subsequently during cardiac surgery (Branthwaite, 1975). Gaseous or particulate emboli, haemodilution and non-pulsatile flow may also contribute to brain damage, despite careful precautions. In spite of many factors involved, data from intraoperative polygraphic recordings in man provide useful evidence concerning thresholds for brain ischaemia.

EEG alterations are common at the onset of bypass with clear deterioration in approximately 63% of patients (Branthwaite, 1973a). Abnormalities appear when MAP decreases to less than a critical value in the region of 50 mm Hg (Junega, Flynn and Berger, 1972; Branthwaite, 1973b) or when the arterio-venous difference is less than 45 mm Hg in children (Harden, 1965). Most resolve in 5 min (Wright et al., 1972). Even with high flow rates, it is suggested that CBF decreases by approximately 50% at the onset of bypass (Branthwaite, 1974). The severity of the EEG abnormality is related consistently to the degree of hypotension (Branthwaite, 1973b; Pronk, 1982) with minor and major abnormalities at MAP of 46 and 37 mm Hg, respectively.

Kriticou and Branthwaite (1977) compared groups of patients before and after the introduction of measures designed to maintain adequate cerebral blood flow (by vasopressors) and prevent microemboli. Although EEG alterations remained frequent, they were usually trivial and neurological deficits decreased from 19.2% to 7.4% or less. Low arterial pressures (33±10 mm Hg at onset of bypass and 24±10 mm Hg in other hypotensive episodes) correlated significantly with EEG abnormality (Prior, Dimitri, Ellis, Etherington, Hinds and Rees, in preparation). When associated relative hypocapnia was avoided, the incidence of EEG abnormalities at onset of bypass was halved. Presumably the hypocapnia had already reduced CBF before arterial pressure decreased with onset of bypass and this increased the risk of cerebral ischaemia. There was some presumptive evidence of autoregulation of CBF, EEG abnormality often being briefer than hypotension. The relative timings were comparable to those obtained by Ekstrom-Jodal (1970) for acute decreases in arterial pressure and suggest that the early EEG recovery may result from cerebral autoregulatory mechanisms. This suggestion was supported by a higher MAP threshold (36±9 mm Hg) for EEG abnormality in older and hypertensive patients than in the remainder (27±10 mm Hg) ($P<0.05$). The negligible effect of hypothermia (20 °C) on autoregulation of CBF suggested by Fox and others (1982) does not suggest lack of risk of cerebral ischaemia. Their MAP are low, but there is insufficient evidence in man to define critical limits for hypothermic subjects. An added difficulty is the similar effect of ischaemia and profound hypothermia on the EEG.

Ischaemic brain damage assessed clinically and neuropathologically is related clearly to low MAP values during operation, prolonged bypass and age. Javid and others (1969) showed that arterial pressures less than 60 mm Hg for 5–132 min (temperature not stated) were followed by neurological deficit, behavioural disturbance and intellectual impairment. These deficits tended to resolve or improve with time in most survivors but, in those who died, histological evidence of cortical infarction and lesser ischaemic alterations were found. Branthwaite (1972) reported episodes of circulatory embarrassment in 24 of 32 patients with neurological deficit after operation. Unfortunately, in the absence of circumstantial evidence from polygraphic recording, it may not be possible to incriminate ischaemia, since gas embolism produces similarly distributed EEG neuropathological changes (Arfel and Naquet, 1974).

Schwartz and colleagues (1973) used intra-operative EEG (recorded by a CFM) to predict either uncomplicated recovery or graded neurological deficit in 100 patients. The predictions were accurate in 83%. Malone, Prior and Scholtz (1981) surveyed all 20 patients, in an 8-year period from the same unit, who had died at any stage after bypass operations and had been examined neuropathologically. CFM abnormalities during operation correlated with the incidence and extent of ischaemic damage which was always of arterial boundary zone distribution. However, a critical degree and duration of CFM depression (at least 7 min major depression) during hypotension was evidently necessary before clinical or histological ischaemic brain damage was found.

Thus, during cardiac surgery, EEG abnormality appears when arterial pressures are too low for the individual; sustained abnormality predicts the occurrence and severity of neurological deficit and ischaemic brain damage.

Carotid artery surgery

Focal cerebral ischaemic damage is a significant risk during the period of carotid clamping necessary for disobliteration or grafting, or both. Ischaemia is not the only cause of brain damage: embolism and hypotension also endanger the patient. Hypotension triggers infarction in many previously well compensated patients with extracranial obstruction of cerebral arteries (Yates and Hutchinson, 1961). Causation of neurological deficit following surgery can often be identified in anaesthetized patients by the timing of EEG abnormalities during or after operation.

The consensus of clinical reports is that when regional CBF after carotid clamping decreases to less than 24–18 ml $min^{-1}/100$ g, EEG abnormalities (slowing and flattening) occur (Trojaborg and Boysen, 1973; Sharbrough, Messick and Sundt, 1973). These are usually reversed immediately by shunting (Sundt et al., 1981), otherwise there is danger of infarction.

Internal carotid artery stump pressures have been considered unreliable indicators for shunting because of the influence of anaesthesia and poor correlation with CBF (McKay et al., 1976). When CBF decreases to less than 18 ml $min^{-1}/100$ g, reversible "physiological paralysis" attributed to local cerebral metabolic changes is observed in patients operated on under regional anaesthesia (Sundt et al., 1977). Experimental evidence suggests that such flows may be tolerated for up to 2 h (in healthy non-arteriopathic subjects) before infarction (Sundt and Michenfelder, 1972; Jones et al., 1981). However, if CBF of 10 ml min^{-1}/100 g, or less, occurs, there is immediate risk of infarction. Obviously, if patients are operated upon under general anaesthesia, the early warning of clinical deficit is not available and the use of EEG as a non-invasive functional monitor becomes necessary.

Conventional multichannel EEG monitoring is limited to a few devoted practitioners because of its complexity; most turn to computer-aided processing (Myers, Stockard and Saidman, 1977; Chiappa, Burke and Young, 1979). The utility of a large amount of intra-operative EEG frequency information is open to dispute. The only EEG sign predicting a poor outcome in one series was voltage attenuation (Chiappa, Burke and Young, 1979). This probably accounts for the success of simpler EEG monitors such as the CFM, provided electrode placement is appropriate. When a pair of ipsilateral centro–parietal CFM leads was used during carotid endarterectomy, changes seen on the 16 channel EEG were identified in nine of 11 patients with regional CBF less than 18 ml min^{-1}/100 g. In the remaining two, the CFM trace was unaltered despite flows of 7 and 15 ml min^{-1}/100 g, and the simultaneous conventional EEG showed only very minor alterations (Cucchiara et al., 1979). About 25% of patients may require shunting during carotid clamping because low flows lead to EEG abnormality. Patients with flows in the range 20–30 ml min^{-1}/100 g may also benefit from shunting to avoid internal capsule ischaemia which may not be revealed by CBF or EEG, both of which essentially reflect cortical function (Sundt et al., 1977). This problem could be addressed by combining EEG monitoring with the use of somato-sensory evoked potentials (Markand et al., 1984) which traverse the internal capsule.

Subarachnoid haemorrhage and intracranial aneurysm surgery

Evoked potentials have been used as measures of ischaemia in patients with subarachnoid haemorrhage. They may be more relevant than EEG because lesions produced by arterial spasm may not extend to the convexity of the brain to become accessible for EEG monitoring. The central somatosensory conduction time (CCT, see above) may be assessed with external electrodes and a small portable averaging computer. Correlations with ischaemia have been demonstrated clinically (Symon et al., 1979).

An alternative technique has been the use of the rather unphysiological "direct cortical response" (Eisenberg et al., 1979). This is a potential elicited by direct electrical stimulation of the cerebral cortex at craniotomy with recording from closely adjacent electrodes. The potential reflects the local CBF and was reduced when MAP was less than 60–70 mm Hg, but still detectable at 37 mm Hg when the underlying electrocorticogram had become isoelectric. The potential faded at pressures below 25 mm Hg, but recovered when MAP was restored. It was proposed as a test of the patient's ability to tolerate controlled hypotension or local ischaemia during intracranial aneurysm surgery.

Head injuries

Two periods of potentially avoidable risk for ischaemic brain damage occur in comatose patients with severe head injuries. Soon after trauma, especially in those with multiple injuries, there is risk of hypoxia and hypotension (Miller et al., 1978). Later, increasing brain swelling, inadequately controlled seizures or perhaps inadequate sedation, may render a poor oxygen delivery insufficient for the metabolic needs of the brain. Neuropathologists have demonstrated over 90% incidence of ischaemic brain damage along arterial boundary zones in patients dying from non-missile head injuries (Graham, Adams and Doyle, 1978). The damage was attributed to reduced perfusion pressure and considered an important cause of mortality and morbidity. This is supported by evidence of increased morbidity and mortality from early hypoxia and hypotension and poorly controlled epilepsy (Price and Murray, 1972; Rose, Valtonen and Jennett, 1977; Miller et al., 1978). Studies of CBF in traumatic coma have shown that ischaemic values (less than 17–20 ml min^{-1}/100 g) occur early after injury, have a fronto–parietal artery boundary zone distribution and are associated significantly with a poor outcome (Overgaard, Mosdal and Tweed, 1981; Overgaard and Tweed, 1976, 1983).

EEG correlates of cerebral ischaemia can be demonstrated by continuous polygraphic recording (fig. 6, table I). When increased intracranial or decreased arterial pressure, or both, critically reduce cerebral perfusion, EEG and cortical evoked potentials decline in amplitude and then become

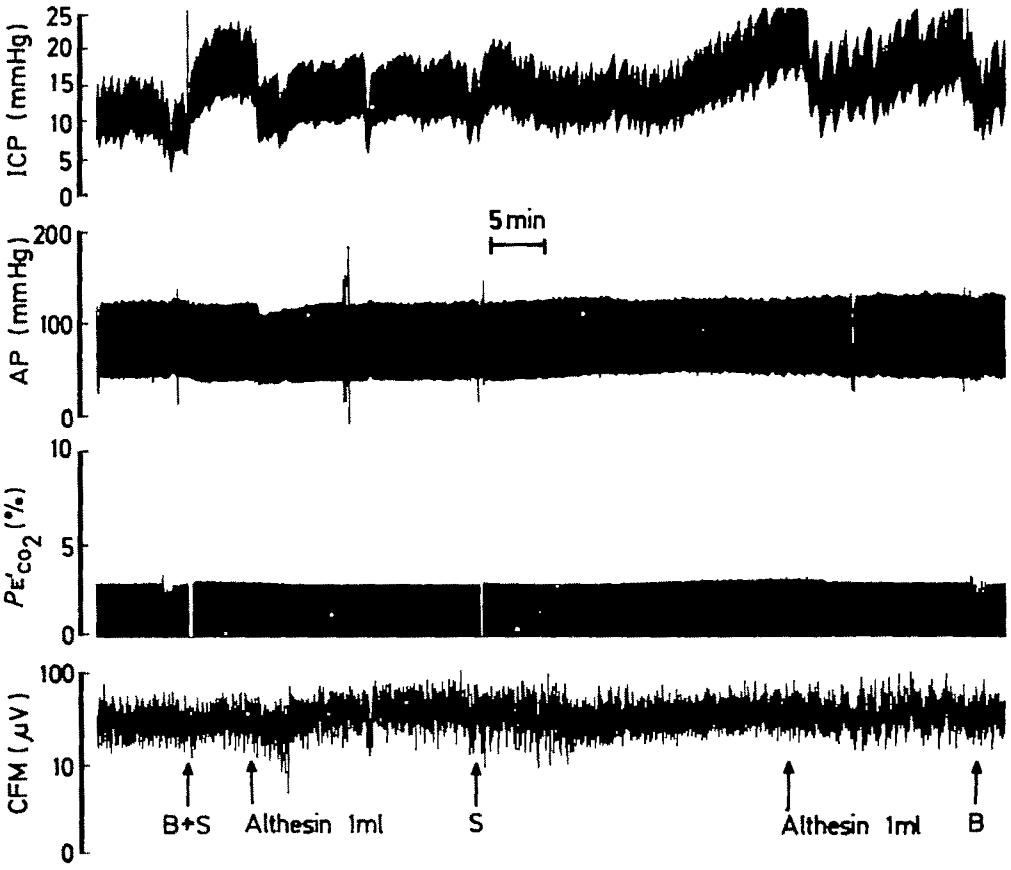

FIG 6. Head injury: polygraphic recording of intracranial and arterial pressures, end-tidal carbon dioxide and CFM in a 7-year-old girl, 3 days after head injury. On admission, extensor responses of right and flexor responses of left limbs. Infusion of Althesin at 6 ml h^{-1} and fentanyl 1 ml h^{-1}; controlled ventilation. Note effects of Althesin boluses (1 ml) and also short term fluctuations in ICP reflected by CFM trace. Subsequent full recovery, returning to school 10 weeks after injury. B=bagging; S=suction.

silent. The mean threshold for EEG depression in eight patients was a CPP of 31±13 mm Hg and that for electrical silence at 24±12 mm Hg (Prior et al., 1982; Prior and Hinds, in preparation). Perfusion pressures of this order leading to electrical silence may be tolerated for several minutes without damage, providing corrective action is taken speedily to restore CBF. Potentials evoked by various modalities of sensory stimulation have an important role in mapping the integrity of specific functional pathways (fig. 4) and are of considerable prognostic value (Greenberg, Becker et al., 1977; Greenberg, Mayer et al., 1977; Hume and Cant, 1981; Lindsay et al., 1981; Narayan et al., 1981; Rappaport, Hall et al., 1981; Rappaport, Hopkins et al., 1981). Evoked potentials are most valuable when prevention or treatment of brain ischaemia involves use of muscle relaxant drugs with controlled ventilation and when major sedatives are used. Unlike clinical neurological testing, none of the evoked potentials depends on a motor response and the short latency components are unique in being virtually unaffected by sedation or anaesthesia sufficient to render the EEG silent (Stockard and Sharborough, 1979; Ganes and Lundar, 1983). The ischaemic thresholds for extinction of evoked potentials in patients with head injury are not yet fully defined.

Correlations between EEG, CBF and oxygen metabolism in the injured brain are difficult because of the direct effects of trauma. EEG signs of local injury, seizure discharges and projected slow-wave abnormalities from brainstem injury (Evans, 1976; Schwartz and Scott, 1978) impinge upon what may be relatively normal background rhythms. The projected slow waves are accompanied by increased brain metabolism and are paradoxical both in terms of arousal mechanisms and EEG/metabolic correlates. Because of such phenomena, EEG must be classified by significant clusters of patterns rather than by single frequency or amplitude measurements. Thus Bricolo and others (1978) and Bricolo, Faccioli and Turazzi (1979) (from a prodigious monitoring study of 1600 comatose patients) grouped EEG according to the presence or absence of "changeability". They have shown variations in associated mortality rates from 8% for a changeable sleep-like, 41% for an alternating to 86% for an unchanging slow pattern and 100% for a silent EEG. Modification of their classification to include EEG responses to painful stimuli has been used for studies correlating EEG with cerebral metabolic rate for oxygen ($CMRO_2$) and regional CBF (Prior et al., 1982; Overgaard, Prior and Rosendal, in preparation). This has revealed a general trend to increasingly impoverished CBF and $CMRO_2$ as the severity of EEG abnormality increases. Most significant was that one-third of regional CBF values were less than 20 ml min^{-1}/100 g and predominantly of arterial boundary zone distribution in the patients with nonreactive unchanging EEG; they all were followed by death or severe disability. Correlative studies between neurophysiological measures and ultimate neuropathology will be of considerable interest.

Seizures and status epilepticus

The increased cerebral metabolism occurring with major seizures leads to ischaemic brain damage if oxygen delivery is insufficient. Intracranial pressure may increase with each seizure discharge (Gabor et al., 1984). Burst firing of neurones produces paroxysmal depolarization with Ca^{2+} entry to neurones reaching toxic concentrations. Increased ATP turnover and mitochondrial metabolism can produce mitochondrial failure with microvacuolation and release of Ca^{2+}. This activates protease and phospholipids and results in ischaemic cell change selectively affecting those neurones most actively discharging (Meldrum et al., 1984; Simon et al., 1984). Prevention of ischaemic damage rests in part on establishing, by EEG monitoring, that all discharges have been abolished by appropriate anti-epileptic therapy.

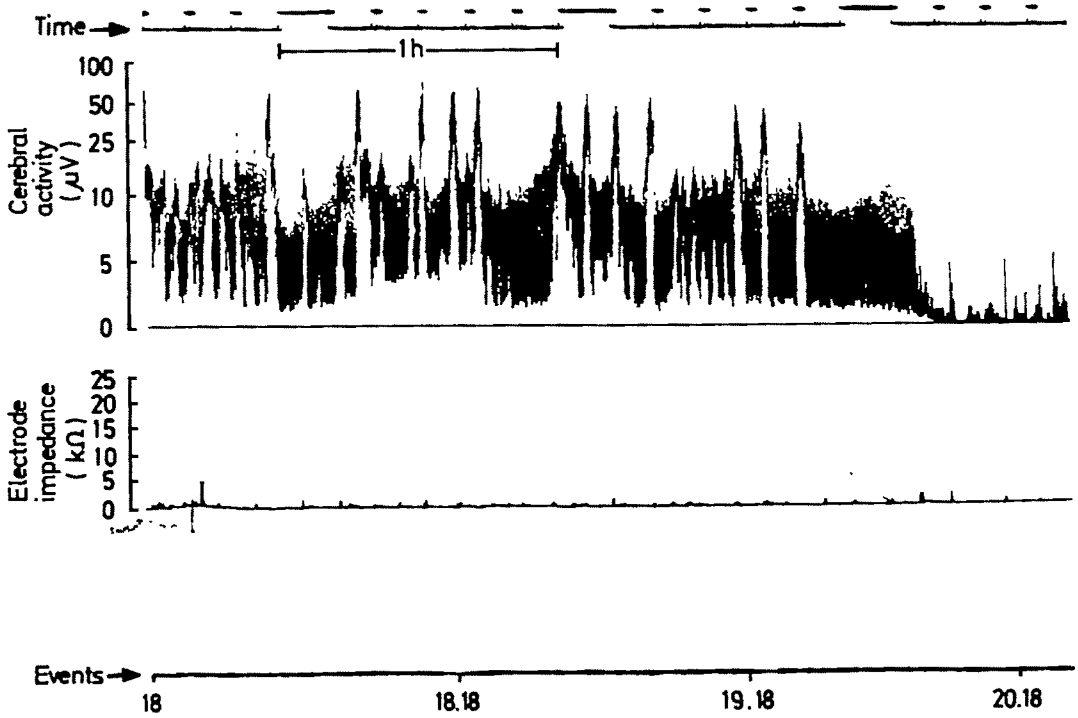

FIG 7. Status epilepticus· CFM recording in a 52-year-old man comatose after severe head and multiple injuries with possible fat embolism Each peak corresponds to a seizure discharge with minor clinical accompaniments. Terminal bradycardia is associated with failure of cerebral perfusion and EEG activity declines towards zero.

Status epilepticus has systemic complications including hyperthermia, hypoxia, hypotension, hypoglycaemia and motor exhaustion that can be avoided by intensive care which includes controlled ventilation and muscle paralysis. This obviates ischaemic damage in the cerebellum. However, unless all seizure discharges are controlled (even though they are not expressed clinically because of muscle paralysis) ischaemic damage still occurs, especially in the hippocampus and cerebral cortex (Blennow et al., 1978). The role of EEG monitoring is thus to determine if paroxysmal electrical discharges have been abolished or to quantify the efficiency of various anti-epileptic drugs (Pampiglione and da Costa, 1975; Eyre, Oozeer and Wilkinson, 1983). Seizure discharges (fig. 7) may be quantified in terms of duration and repetition rate. The longer clinical convulsions or electrical discharges last, the greater is the likelihood of brain damage (Rowan and Scott, 1970; Oxbury and Whitty, 1971; Aminoff and Simon, 1980).

Cardiac arrest

The occasions when EEG monitoring is in progress at the time of cardiac arrest and resuscitation must be relatively few. However, there is evidence that the duration of the electrical silence that follows total cerebral circulatory arrest is related inversely to the quality of outcome. In a personal series of 371 patients (916 EEG), studied soon after resuscitation, 149 had isoelectric EEG. Of these, only two (with drug overdose) recovered fully; two survived in vegetative states and the remainder died. Clinical and neuropathological examination in 24 gave evidence of a typical distribution of damage affecting the neocortex but not the brainstem. EEG and evoked potential abnormalities are consistent with the severity and distribution of ischaemic damage (Lindgren, Petersen and Zwetnow, 1968; Brierley et al., 1971; Prior, 1973; Trojaborg and Jørgensen, 1973; Starr, 1975; Uziel and Benezech, 1978).

In an important study of all episodes with circulatory arrest over an 8-year period in two Copenhagen hospitals, Jørgensen and Malchow-Møller (1981) examined 613 patients. The circulation was successfully restarted in 329; after exclusion of patients with overdose or with pre-existing cerebral abnormalities, there remained 125 who had no detectable EEG immediately after resuscitation. These latter patients were followed with EEG monitoring and serial neurological assessment. An orderly sequence of recovery of EEG features and related neurological signs was observed in patients recovering (table II). Whilst the EEG remained isoelectric, first the pupils became smaller, then all cranial nerve reflexes except the caloric–vestibular returned. Next, motor responses appeared, predominantly decerebrate (extension of all limbs and neck) posturing. At this stage intermittent EEG activity appeared, followed by medium sized pupils, decorticate (flexion of the upper and extension of the lower limbs) posturing and stereotyped reactivity to stimuli (repetitive grimacing, eye movements, swallowing, yawning, chewing, respiratory alterations, or other movements without defence or escape characteristics). Next the EEG became continuous whilst stereotyped responses persisted; consciousness was then regained and basic motor, sensory and mental

TABLE II. *Cardiac arrest: data based on Jørgensen and Malchow-Møller (1978, 1981) with permission, to indicate longest interval after resuscitation for various clinical and* EEG *signs to appear if the patient is going to recover (a) any function, (b) consciousness or (c) full restoration of all their faculties within 1 year. (Descriptions of terms are given in the text)*

	Longest delays (from time of resuscitation) for appearance of clinical or EEG features compatible with:		
Clinical and EEG features	(a) any functional recovery	(b) recovery of consciousness	(c) full recovery by 1 year
Respiratory movements	15 min	7 min	
Pupillary light reflex	28 min	12 min	
Coughing/swallowing reflex	58 min	23 min	
Caloric vestibular reflex	15 h	2 75h	
Decorticate posturing	9 h	3 h	
Stereotyped reactivity	7.5 h	3 h	
EEG – intermittent	7.5 h	3.3 h	3 h
EEG – continuous	17 h	10.5 h	
Consciousness			2 days
Speech			6 5 days
Coping with personal needs			2 weeks

faculties returned gradually. In contrast, brain death could be predicted by cranial nerve areflexia with loss of spontaneous respiratory movements, often accompanied by dilated pupils, spinal reflexes, poikilothermia and diabetes insipidus (see also Jennett, 1981; Pallis, 1983). Intermittent or continuous EEG activity containing sharp waves or spikes and extension or flexion reflexes predicted an unfavourable outcome. In such patients, some cranial nerve reflexes usually recovered with the abnormal EEG activity; both might disappear abruptly or regress in a pattern reversing the order of their earlier recovery. Such deterioration was always secondary to cardiovascular or pulmonary complications. The neuropathological examinations in this large series showed extensive neuronal loss when adverse EEG and clinical signs had persisted for more than 72 h.

EEG AND EVOKED POTENTIAL MONITORING DURING TREATMENT OF BRAIN ISCHAEMIA

The treatment of brain ischaemia is primarily preventative: prevention of the original insult and prevention of its consequences which may lead to a chain of events that worsen brain damage. Neurophysiological monitoring has a role in both. The brain may be "protected" by reducing the metabolic needs to the levels available (by hypothermia, anaesthesia or sedation), preventing high demands (control of seizures, avoidance or blocking of painful and other stimuli), and ensuring optimal oxygenation and perfusion (controlled ventilation, maintenance of fluid volume, arterial pressure and reduction of increased intracranial pressure).

EEG monitoring ascertains the level of sedation achieved and identifies when stimulus-induced arousal responses increase metabolic demands. It permits recognition of seizure discharges even when clinical accompaniments are masked by drugs and indicates when reduction of cerebral perfusion has become critical. It helps to guide the administration of boluses of sedatives before painful procedures in intensive care (Kassell et al., 1980; Prior et al., 1983). Experimental observations (Michenfelder, 1974) suggest that such boluses have no effect on intracranial pressure if a silent EEG is present (indicating that maximal metabolic depression already exists). Studies in man with etomidate boluses (Bingham, Procaccio, Hinds and Prior, in preparation) and Althesin (Procaccio, Bingham, Hinds and Prior, in preparation) lend support to this view.

Evoked potentials are useful as an adjunct to EEG monitoring when treatment involves massive sedation. This abolishes motor function and EEG, but does not affect the short latency auditory brainstem and somatosensory evoked potentials (Stockard and Sharbrough, 1979; Sutton et al., 1982; Ganes and Lundar, 1983).

Hypothermia affects the BAEP with increase in wave V-I latency of the order of 4–6% per °C cooling (Marsh, Yamane, and Potsic, 1984); these authors comment that such prolongation "does not inevitably reflect a pathological state. Rather it is an expression of a lawful relationship between temperature and the rate of electrochemical processes underlying nerve conduction and synaptic process". In contrast, with the SSEP, whilst peripheral nerve sensory conduction velocity decreases during cooling by 2 $\mathrm{m\ s^{-1}\ {}^{\circ}C^{-1}}$, CCT is reported to be unaffected (Gilmore and Lastimosa, 1984).

During intensive treatment of a patient whose brain has been ischaemic it is important to differentiate between those electrical abnormalities produced by damage already inflicted, those from depression by therapeutic agents or hypothermia and those induced by continuing low perfusion states. It is here that a combination of neurophysiological techniques aids management and prognostication.

CONCLUSIONS

Monitoring of EEG and evoked potentials is indicated when there is risk of cerebral ischaemia during elective procedures and to provide information on the functional state of the central nervous system during treatment of comatose patients.

When EEG power or amplitude begins to decrease or evoked potential latencies increase, it does not follow that brain damage has occurred. It is a warning that cerebral blood flow or oxygen delivery is impaired and that the patient is at risk of ischaemia and time is limited. Damage occurs after several minutes of electrical silence.

The most effective monitors display continuous amplitude of EEG, filtered to exclude potentially artefactual slow waves. They also indicate frequency content, for example in a combined power–amplitude display.

During surgical procedures such as cardiopulmonary bypass or induced hypotension when global cerebral ischaemia is a risk, bilateral EEG monitoring is appropriate. For warning of focal ischaemia (for example during carotid artery surgery), appropriately lateralized recording should be compared with control data from the contralateral hemisphere. If risk of ischaemia is mainly to subcortical structures (e.g. after subarachnoid haemorrhage), somatosensory evoked potential are more helpful than EEG.

In comatose patients, EEG monitoring warns of impending ischaemia when a critical reduction of cerebral perfusion occurs and also allows recognition of increased metabolic demands, for example with seizure discharges or marked reactivity to pain.

Evoked potentials are indicated for mapping the integrity of various sensory pathways after trauma and as a means of assessing central nervous function when clinical and EEG signs are depressed by major sedatives.

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BARBITURATES IN BRAIN ISCHAEMIA

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The role of barbiturates as the prototypical pharmacological neuroprotective drugs has emerged over the past three decades from demonstrations that they extend rudimentary neurological function during severe hypoxia, limit the area of infarction following cerebral vascular occlusion, and reduce intracranial pressure under a variety of circumstances. Most studies indicate that very high doses of barbiturates are required to elicit a protective effect. This can result in severe depression of brain function and other excitable tissues throughout the body, in addition to cardiovascular instability and respiratory depression. While the search for non-anaesthetic drugs with neuroprotective actions is actively pursued, evaluation of barbiturates continues, for protection against different forms of cerebral ischaemia. Within this context, this paper reviews the relevant pharmacology of barbiturates used in high doses to prevent neuropathology in brain ischaemia. Also discussed are laboratory and clinical trials of barbiturates during hypoxia, focal and global ischaemia and intracranial hypertension. A closing section indicates the guidelines involved in applying continuous high-dose barbiturate therapy in management of patients.

Cerebral effects of barbiturates

The most obvious central nervous system effect of barbiturates is a dose-dependent reversible depression of neurological function (Harvey, 1980). While the precise mechanism(s) of this effect remains unknown, it clearly involves interference with synaptic transmission and multineuronal networks and to a lesser extent a direct local anaesthetic influence upon membrane structures (Harvey, 1980). Some evidence also points towards an indirect effect of barbiturates on neurotransmission. They may enhance presynaptic inhibition by facilitating the binding of gamma-aminobutyric acid (GABA) to GABA-specific sites regulating neuronal ionic conductance (Higashi and Nishi, 1982; MacDonald and MacLean, 1982). It is also recognized that different structurally specific brain target sites are involved in the anaesthetic and anticonvulsant activities of barbiturates which display both these activities (Andrews and Mark, 1982). This may explain the ability of phenobarbitone to exert a strong anticonvulsant action with minimal sedation, while thiopentone and pentobarbitone exhibit anticonvulsant properties at doses associated with a high degree of sedation (Harvey, 1980; MacDonald and McLean, 1982).

Associated with barbiturate brain function depression is a parallel dose-dependent reduction in cerebral metabolic rate (CMR) and blood flow (CBF). These CBR and CMR effects plateau at the point where electroencephalographic (EEG) activity becomes isoelectric. This suppression of synaptic activity is associated with maximal reductions in CMR (for oxygen) and CBF of approximately 50% (Pierce et al., 1962; Michenfelder, 1974). Barbiturate-induced reductions in CBF are accompanied by increases in cerebral vascular resistance and reductions in cerebral blood volume, and this presumably explains their action in reducing intracranial pressure (ICP) (Shapiro, 1975). The cerebrovascular resistance increase from barbiturates is associated with metabolically mediated direct or indirect (neurogenic) vascular events, or both, since direct application of pentobarbitone to isolated cerebral vessels reduces their contractile response (Edvinsson and McCulloch, 1981; Marin, Loboto and Rico, 1981). Cerebral blood flow and metabolic rates are distributed heterogeneously throughout the brain and barbiturates cause non-uniform alterations in local flow and metabolism in different struc-

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tures (Shapiro et al., 1975).

A popular explanation for the cerebral protective action of barbiturates relates to their ability to depress brain metabolism during periods of critically low CBF. As noted above, CMR depression by barbiturates has a baseline effect when the EEG is already isoelectric and synaptic activity has ceased (Michenfelder, 1974). Reductions in cerebral metabolism below the isoelectric threshold may be obtained with techniques acting not only on synaptic activity: for example lignocaine (impedes membrane ionic flux), ouabain (blocks ionic pumps), and hypothermia (slows chemical reactions) (Astrup, Sorensen and Sorensen 1981a, b). Combinations of barbiturates with lignocaine or hypothermia, or both, are additive with regard to CMR depression (Lafferty et al., 1978; Hagerdal et al., 1979; Astrup, Sorensen and Sorensen, 1981b). However, when the EEG is already isoelectric from extreme hypothermia (18 °C), the addition of barbiturates does not reduce metabolism further (Steen et al., 1983).

Subcellular biochemical events which characterize barbiturate anaesthesia include a reduction in glycolytic flux accompanied by increased tissue concentrations of glucose, glucogen and phosphocreatine (Strang and Bacheland, 1973; Carlsson, Harp and Siesjö, 1975; Siesjö, 1978; Benzi, Agnoli and Dagani, 1979; Harvey, 1980). Maintenance of a normal energy charge potential (of adenine phosphate compounds) indicates that barbiturate anaesthesia does not result from energy deprivation, but rather from blockade of neuronal transmission (Siesjö, 1978). When CMR oxygen is reduced by 50% with thiopentone, glycolytic flux is retarded at the phosphofructokinase step (Carlsson, Harp and Siesjö, 1975). While confirming phosphofructokinase inhibition during beta frequency EEG discharges, other studies indicate a shift toward reduced hexokinase activity at deeper levels of anaesthesia (Krieglstein and Sperling, 1981). Hexokinase inhibition is postulated to result from barbiturate solubilization of membrane binding of the enzyme (Krieglstein and Sperling, 1981). Other metabolic changes include reduced flux and pool size in the citric acid cycle and alterations in amino acid ratios secondary presumably to reduced delivery of pyruvate (Carlsson, Harp and Siesjö, 1975).

BARBITURATES AND PROTECTION AGAINST CEREBRAL ISCHAEMIA. PREVENTION AND TREATMENT

For the purposes of the following discussion *prevention* is defined as therapy administered before an anticipated ischaemic episode that limits subsequent neuronal loss or infarction. *Treatment* consists of therapy begun after or during brain ischaemia which limits the pathological consequence of the ischaemic insult. Ischaemia occurs whenever metabolic demands are not coupled with blood flow sufficient to prevent a shift to anaerobic metabolism. Within this context, relative ischaemia occurs whenever an increase in metabolism outstrips compensatory blood flow increases and there is a resultant loss of aerobic metabolic capacity. Prolonged generalized seizure activity is an extreme example of this situation.

Numerous theories have emerged to explain the ability of barbiturates to prevent or treat brain ischaemia under a variety of circumstances. Definitive proof has not emerged for a single protective mechanism of barbiturates, and it is possible that a combination of actions may prevent or reduce the effects of cerebral ischaemia in specific disease states. Presently, most therapeutic approaches to treatment of ischaemic brain are based upon the principle of improving the ratio of oxygen supply to oxygen demand (Steen and Michenfelder, 1980).

Barbiturate therapy for acute ischaemic brain disease can improve this ratio via its anticonvulsant, metabolic and cerebral vascular effects. Reduction of CMR is probably responsible for prolonged survival of animals under lethal hypoxic conditions (Wilhjelm and Arnfred, 1965; Steen and Michenfelder, 1979; Artru and Michenfelder, 1981). Similarly, suppression of normal or hypermetabolic conditions, or both, in the border zone ischaemic tissues (penumbra) surrounding a brain infarct produced by occlusive vascular disease improves the oxygen supply:demand relationship. Barbiturate-related increases in vascular resistance in non-diseased areas of the brain may shunt flow into regions of critically reduced CBF in focal cerebral vascular disease. The same vascular action in situations of intracranial hypertension can decrease ICP, increase the overall cerebral perfusion pressure (CPP = AP − ICP), and shunt blood into flow-compromised areas. Seizures related to ischaemia are potentially dangerous, since flow is already compromised and the metabolic demand is extremely high. In this situation, the anticonvulsant action of barbiturates is probably the paramount protective mechanism (Michenfelder, 1982; Todd et al., 1982).

Molecular mechanisms of barbiturate protection are more controversial, as a result partly of incomplete understanding of the critical molecular events leading to ischaemic tissue death. They include stabilization of lysosomal membranes, quenching of free radical reactions, and reduction of intracellular calcium concentrations and modified amino acid or neurotransmitter release (Steen and Michenfelder, 1980). Among barbiturates, only thiopentone has significant free radical scavenging properties (Smith, Rehncrona and Siesjo, 1980).

Specific Applications of Barbiturate Protection

Hypoxia

Laboratory. Twenty years ago, several anaesthetic agents were found to have a protective action in mice breathing 5% oxygen in nitrogen (Arnfred and Secher, 1962; Wilhjelm and Arnfred, 1965). In this model, protection consisted of prolonged survival as determined by observation of last gasp activity. Although several anaesthetics conveyed protection in this model, barbiturates emerged as conferring significantly greater protection (Wilhjelm and Arnfred, 1965). More recent studies with the hypoxic mouse model indicate that it is the anaesthetic action of barbiturates rather than brain barbiturate concentration that is associated with protection (Steen and Michenfelder, 1979). In mice rendered tolerant to barbiturates, the hypoxic survival curve was shifted to the right; that is, higher doses were required to obtain the same protection (Steen and Michenfelder, 1979). Hypothermia alone also increases survival times, and the addition of either pentobarbitone or phenytoin to moderate hypothermia further improves survival (Steen and Michenfelder, 1980; Artru and Michenfelder, 1981). Further support for this concept is that barbiturate suppression of functional brain activity, rather than a direct molecular action is protective and is drawn from tissue culture studies of hypoxic neurones. Anoxic exposures of mature hippocampal cell cultures resulted in neuronal death, unless synaptic transmission was inhibited by magnesium (Rothman, 1983). It appears that any manoeuvre impairing normal or excess neurotransmission should have a role in protecting ischaemic brain.

While the hypoxic mouse model provides a screening procedure in recognition of drugs with a very specialized protective action, it gives us little more information than recognizing an anaesthetic effect (with related CMR depression) and has no direct clinical application. Retention of last gasp activity is a complex event. Besides relating to a cerebral protective effect it may also reflect respiratory and cardiovascular actions of the drugs tested. The model is also critically dependent upon temperature and the degree of hypoxia. Too much oxygen and all survive; too little oxygen and all die, without regard to the drug being evaluated. Extrapolation of any protective action in this model to clinical cerebral ischaemia should be tempered by recognition of its evanescent protective actions over an extremely narrow range of tissue ischaemia.

Focal ischaemia

The ability of barbiturates to reduce the expected area of cerebral infarction has been documented repeatedly under a variety of experimental conditions associated with focal brain ischaemia. The number of variables influencing the outcome of individual studies are many and include the dose, timing and duration of administration of the barbiturate, in addition to the permanent or transient nature of the cerebral vascular occlusion, species selected for study, vascular anatomical variables, incidence of seizures, and cardiovascular responses. Procedures calling for permanent vascular occlusion relate to the clinical stroke syndrome, while those associated with transient occlusive periods may provide anaesthetic management guidelines during cerebral vascular reconstructive surgery.

Acute focal ischaemia results in unpredictable heterogenous changes in local CBF and time-dependent neuronal injury (Garcia, 1984). Survival of focally ischaemic tissue appears to depend upon maintaining a critical balance between blood flow and metabolism. In focal ischaemia, barbiturates are believed to accomplish this by reducing metabolism and improving collateral flow. Other drugs (calcium blocking agents, lignocaine, etc.) which reduce metabolism and techniques aimed at improving collateral flow to ischaemic tissue are available (Shapiro, 1984; Gisvold and Steen, 1985). These may share some common mechanisms with barbiturates and include decreasing ischaemic vasospasm, reducing cerebral oedema, improving CBF rheology, decreasing ICP, and antiprostaglandin and antiplatelet activities (Garcia, 1984). Increasing local cerebral perfusion pressure by increasing arterial pressure and shunt devices remain the mainstay of intraoperative brain protection.

Laboratory. During acute middle cerebral artery occlusion, measurement of cerebral oxygen availability revealed an increase in the flow:metabolism ratio in ischaemic cortex produced by barbiturates (Feustel, Ingvar and Severinghaus, 1981). Local cerebral blood flow studies under similar experimental conditions suggest that the increase in oxygen availability relates to a homogenizing influence of barbiturates on CBF distribution in ischaemic cortex (Branston, Hope and Symon, 1979). Brain intracellular pH during focal ischaemia decreases less in barbiturate-anaesthetized monkeys than in those given halothane (Anderson and Sundt, 1983). While this may represent barbiturate protection, it could also result from a direct toxic or CBF effect of halothane (Michenfelder and Theye, 1975). Barbiturates prolong the duration of evoked potential activity in ischaemic primate cortex, but have no effect on the ischaemic threshold for intracellular potassium efflux (Branston, Hope and Symon, 1979; Astrup, Siesjö and Symon, 1981). Prolongation of evoked potentials represents protection of brain function as it relates to CMR, while potassium efflux is considered a sign that cellular homeostasis is threatened.

Barbiturates given before or following permanent cerebral vascular occlusion have been shown to reduce significantly the area of infarction in a number of species (Smith et al., 1974; Moseley, Laurent and Molimari, 1975; Michenfelder, Milde and Sundt, 1976; Selman et al., 1981b). A few reports suggest that the use of barbiturates may increase the area of infarction when the vascular occlusion is permanent and barbiturates cause hypotension, which limits development of collateral flow (Rockoff, Marshall and Shapiro, 1979; Selman et al., 1981b).

In primates subjected to permanent middle cerebral artery occlusion, the reduction in infarct size was proportional to the dose of barbiturate and effective treatment could be demonstrated when institution (Levy and Brierley, 1979; Hoff et al., 1975) of therapy was delayed from 30 min to 2 h (Smith et al., 1974; Moseley, Laurent and Molimari, 1975; Michenfelder, Milde and Sundt, 1976; Tamura et al., 1979; Selman et al., 1981b; Spetzler et al., 1982). Several studies in animals with permanent cerebral vascular occlusions indicate that protective mechanisms other than CMR reduction may contribute to reduction in infarct size. In comparative studies in cats, the same degree of cerebral protection was obtained during MCA occlusion with pentobarbitone and imidazole derivative (Tamura et al., 1979; Ochiai et al., 1982). Equal degrees of infarct reduction in these experiments were obtained despite considerably less CMR depression by the imidazole, and in the absence of a barbiturate-induced flow increase in the ischaemic cortex. When pentobarbitone and hypothermia are compared at concentrations resulting in similar CBF and CMR effects, only the barbiturate significantly reduced ischaemic cerebral oedema in monkeys with MCA occlusion (Simeone, Frazer and Lawner, 1979). Thus protective mechanisms probably exist in addition to the cerebral haemodynamic and metabolic influences upon focally ischaemic brain tissue.

Barbiturates also have protective effects in models of focal cerebral ischaemia in which a transient period of vascular occlusion is followed by recirculation (Levy and Brierley, 1979; Selman et al., 1981b). While it seems reasonable to expect that barbiturate protection conferred during permanent cerebral vascular occlusion would also extend to transient occlusion, the additional factor of reperfusion into zones of previously severely ischaemic tissue needs consideration. In situations of relatively short occlusion, such as those associated with vascular reconstructive surgery, no additional problems should be expected. However, when flow is restored to an area that has begun the process of infarction, recirculation may enhance oedema and haemorrhagic infarction (Selman et al., 1981b). In a series of baboons subjected to either permanent or transient MCA occlusion, reperfusion after 6 h of cerebral ischaemia was more detrimental in the absence of protective measures than continued occlusion (Selman et al., 1981b). In these experiments, when the same period of occlusion was followed by reperfusion, barbiturate-induced coma maintained (started 30 min after occlusion) for 96 h, provided nearly complete protection. Barbiturate dose was adjusted to maintain the EEG potential at less than 2 μV and with arterial pressure maintained within 15% of control. Intracranial hypertension was prevented only in the group treated with this procedure. In a similar series of laboratory therapeutic trials, high dose barbiturate anaesthesia, begun 30 min following MCA occlusion and maintained during an extracranial to intracranial vascular shunting procedure, appeared to confer protection (Spetzler et al., 1982).

Clinical. While the concept of brain protection by barbiturates during focal cerebral ischaemia seems established by laboratory studies, clinical experience has been *very* limited and anecdotal. A compelling reason for slow translation of positive animal findings into clinical practice relates to the reluctance of clinicians to subject the older population, prone to stroke, to the dangerous side effects and intensive supportive care required with high-dose barbiturate therapy. Also, many occlusive stroke patients remain conscious despite severe focal neurological deficits. In a series of four patients with inadvertent permanent intraoperative MCA occlusion treatment promptly with 5 days of high-dose barbiturate therapy, all died of intracranial hypertension which developed when the barbiturates were discontinued (Rockoff, Marshall and Shapiro, 1979). In untreated patients with the same lesion, increased intracranial pressure developed approximately 2 days earlier and was the cause of death. Thus, it appears that barbiturate therapy retarded processes relating to formation of cerebral oedema or loss of cerebral vasomotor control, or both. This mechanism may be important in naturally occurring clinical stroke with a great potential for development of collateral blood flow and dissolution of embolic occlusion. In the four patients in the study described above, reperfusion and collateralization potential was absent because the occlusive agent was intravascular embolization of a polymer material (Rockoff, Marshall and Shapiro, 1979). More recently, a patient with severe eclampsia complicated by hemiplegia and intracranial hypertension made an excellent neurological recovery after 12 days of high-dose barbiturate treatment (Caseby, 1983).

The most frequent potential clinical application of barbiturate therapy for protection during focal ischaemia occurs during extra- and intracranial revascularization procedures. In this instance, anaesthesia is usually required, thereby reducing the additional risk to the patient. Most procedures suggest maintenance of high concentrations of barbiturate for periods less than the duration of the total surgical procedure and this further limits the risk. While reduced risk may be inherent in the intraoperative use of barbiturate therapy, determination of the risk:benefit ratio may be very difficult. This problem is compounded by the existing low incidence of neurological morbidity and mortality in correctly selected patients operated upon by experienced and skilled surgeons. Further complicating the problem of evaluating the efficacy of intraoperative barbiturate therapy, is that the suggested dose schedules are very different from those found necessary in the laboratory and without substantiation of their clinical effect. Table I lists various objectives and dose ranges associated with intraoperative use of barbiturates. For example, many centres use thiopentone 4–5 mg kg^{-1}, administered just before internal carotid artery occlusion during carotid endarterectomy. This results in an average period of 5 min of EEG burst-suppression, while the carotid occlusion period is up to five times longer in duration (Moffat et al., 1983). It is possible that local CMR depression by barbiturate retention within poorly perfused brain areas persists and is not detected by the surface EEG electrodes. This might result in locally reduced metabolism which could result from either uncleared barbiturate or ischaemia, or both. In addition, preferential shunting of blood from barbiturate-induced cerebral vasoconstriction in well perfused tissue is not possible for prolonged periods as a result of almost immediate washout of the drug. In this milieu, it appears that an extraordinarily large prospective study will be required to establish the intraoperative efficacy of barbiturate protection.

When intracranial microvascular procedures are performed, more sustained blood barbiturate concentrations are usually suggested since the occlusion periods are longer and the potential for sufficient collateral circulation less than with carotid endarterectomy. There are isolated reports of barbiturate protection during temporary intracranial vascular occlusion for aneurysm surgery, in addition to extracranial–intracranial shunting procedures (Hoff, Pitts and Spetzler, 1977; Spetzler et al., 1982). In one of these patients operated on under thiopentone anaesthesia (46 mg kg^{-1}/5 h) a marked hemiparesis developed 48 h after operation as a result of a clotted shunt (Spetzler et al., 1982). Removal of the clot, again under barbiturate protection, resulted in

TABLE I. *Intraoperative use of thiopentone therapy*

Load (mg kg^{-1})	Time (min)	Maintenance (mg kg^{-1} min^{-1})	Peak (μg ml^{-1})	Indication	Author
2–2.5	—	1–1.5	38–42	Anaesthesia	Becker and others (1977)
4	3	—	20	Burst-suppression	Moffat and others (1983)
10	10	—	—	Vascular surgery	Spetzler and others (1982)
75	60	0.1–0.2	80	Vascular surgery	Todd and others (1982)

resolution of the hemiparesis. While resolution of the deficit may have been unlikely without re-operation, the role of barbiturates in this process cannot be established without further systematic clinical studies.

At present, it is difficult to suggest specific guidelines for the intraoperative use of high doses of barbiturates for brain protection during revascularization. However, at least two different approaches are possible, based on different rationales. The first approach (favoured by this author) consists of identifying high risk patients by trial vascular occlusion (of at least 5 min) with EEG monitoring. If this occlusion results in EEG abnormalities that cannot be corrected by a temporary shunt or if a shunt is not technically feasible, or both, then barbiturates may be administered. They should be given after the temporary test occlusion has been released and the EEG returns to its normal baseline. If the EEG does not recover, the occurrence of an embolic event is presumed and high dose thiopentone should be sustained for a longer period than described below. Protection for temporary vascular occlusion should be achieved with thiopentone given in doses sufficient to achieve an isoelectric EEG or burst suppression patterns, or both. Drug administration continues for the duration of occlusion and then ceases. A grossly asymmetric EEG pattern on emergence in a previously normal patient suggests intraoperative brain ischaemia and barbiturates should be recommenced as diagnostic studies or reoperation, or both, is initiated. Administration of fluids i.v. and vasopressors are used to maintain arterial pressure, to within 30% of the highest baseline ranges obtained before operation.

The second approach to the use of barbiturates for prevention of brain ischaemia during revascularization surgery assumes that these drugs always provide a greater margin of safety than the risks involved in their use. In this instance they are used routinely before clamping with or without a test occlusion period or plans to use a shunt device. The guidelines for the administration schedule remain the same as noted above. This author does not know of any laboratory trial indicating that a single dose of thiopentone given to achieve a very short (5–10 min) EEG burst suppression period is sufficient to provide protection against brain ischaemia of significantly longer duration (Moffat et al., 1983). In the absence of such studies, it is premature for generalized clinical application of high dose barbiturate therapy for brain protection for permanent or transient focal ischaemia (Yatsu, 1982).

Global brain ischaemia

Before discussing the available data describing application of barbiturates in the treatment of global cerebral-anoxic-ischaemic insults, it is important to define the relationship of the timing of therapy to the aims of treatment. Presumably, when barbiturates are given immediately following a cardiac arrest, they are administered to block pathophysiological events leading to neuronal death. Following neuronal death, brain swelling may occur and barbiturates could be administered to reduce intracranial pressure, and block further compromises of cerebral perfusion pressure. However, intracranial hypertension following cardiac arrest is a late occurrence and denotes widespread neuropathology and usually does not result in brainstem compression (Graham, 1985). This circumstance will be reviewed under intracranial hypertension control, while the data discussed here relate to the immediate prevention of neuronal death.

Laboratory. An important study on barbiturate protection during global brain ischaemia, published in 1966, indicated that pentobarbitone anaesthesia before the insult was protective (Goldstein, Wells and Keats, 1966), but these results could not be reproduced by another laboratory using the same model with brain ischaemia produced by aorto–vena caval clamping (Steen, Milde and Michenfelder, 1979).

In 1978 a report was published indicating that massive doses of barbiturate administered after 16 min of selective cerebral circulatory arrest ameliorated brain damage (Bleyaert et al., 1978). This study obtained selective cerebral circulatory arrest by using a high pressure neck tourniquet, deep halothane anaesthesia, ganglionic blockade and positive airway pressure. Assessment of CBF was not peformed in individual animals and the chance of partial reperfusion during the arrest period could not be excluded. In addition, different programmes of supportive care were used for the control and treatment groups (Bleyaert et al., 1978; Rockoff and Shapiro, 1978). When the study was repeated in the same laboratory with control of these factors, no benefit from thiopentone was found (Gisvold et al., 1984). Another group used ventricular fibrillation followed by resuscitation and a prolonged period of intensive care (Todd et al., 1982). They found increased survivors among the thiopentone treated animals and this was attributed to suppression of seizures. However, the surviving treated animals had the same degree of neurological impairment as the untreated controls. While this study supports the concept that postcardiac arrest therapy may influence neurological outcome, it does not necessarily indicate that barbiturates are required. Other anticonvulsants, with less profound brain depressant and circulatory effects, may accomplish the same goal at reduced risk.

The conclusion emerging from most global cerebral ischaemia resuscitation studies is that immediate post-resuscitation supportive care (including rapid restoration and maintenance of cerebral perfusion pressure and normal arterial blood-gas tensions) can influence neurological outcome (Gisvold et al., 1984). Other therapeutic approaches aimed at limiting post-arrest brain pathophysiology include correction of late perfusion abnormalities and blocking biochemical pathways leading to autolysis or formation of toxic metabolites (Shapiro, 1984).

Only one prospective randomized clinical trial of thiopentone loading following cardiopulmonary arrest has been accomplished (Abramson et al., 1983). This international co-operative study examined 281 patients and found no difference between the thiopentone-treated patients and those receiving standard post-arrest care. Thus, the clinical findings are in agreement with the laboratory data and do not support the use of barbiturates after resuscitation from cardiac arrest.

Intracranial hypertension

Uncontrolled intracranial hypertension causes focal or global reductions in cerebral perfusion pressure resulting in localized or generalized cerebral ischaemia, or both. Severely increased ICP is encountered most commonly in head injured patients. When ICP persistently exceeds 25 mm Hg in this group of patients, mortality ranges from 80% to 100% (Marshall, Smith and Shapiro, 1979a; Miller, 1979; Saul and Ducker, 1982). Successful attempts to reduce severely increased ICP correlate with improved outcome (Becker et al., 1977). The ability of barbiturates to reduce increased ICP probably represents the major protective mechanism in intracranial hypertension. In addition, the protective mechanisms outlined for focal ischaemia may also apply when the ICP is high, since scattered regions of low CBF also exist.

Laboratory. Precise laboratory models for intracranial hypertension complicating head injury or infectious disease are not available. However, laboratory models resulting in one or more of the pathological processes recognized in clinical cases of intracranial hypertension have been developed. These pathophysiological conditions include cerebral vasomotor paralysis, cerebral oedema and acute hydrocephalus. When cerebral vasomotor paralysis is present, swelling of the intravascular blood compartment occurs (Langfitt, 1968). This can develop suddenly, with stimulation of certain brain areas, or more gradually during expansion and deflation of an extradural balloon. Barbiturates have been found to be effective in reducing increased ICP secondary to vasoparalysis or cerebral oedema, or both (Langfitt, 1968; Ischii, 1976; Smith and Marque, 1976). This therapeutic action is presumed to result from increase in cerebral vascular resistance which reduces cerebral blood volume and may also reduce vasogenic cerebral oedema by increasing proximal arteriolar resistance or reducing systemic arterial pressure, or both. The timing of administration of barbiturates may be important in relation to the pathophysiological phase of the intracranial hypertension. When barbiturates are administered before deflation of an extradural balloon, cerebral perfusion pressure decreases without a reduction in ICP (Bricolo and Glick, 1981). Thus if therapy is initiated at a stage when the cerebral vasculature is compressed by an extradural haematoma, arterial hypotension caused by the drug may increase the tendency to develop cerebral ischaemia.

Clinical. In the 1930's, several reports indicated that administration of barbiturates to patients resulted in either a reduction or no increase in cerebrospinal fluid (CSF) pressure (Butler, 1936; Horsley, 1937; Gurdjian, Webster and Sprank, 1939). This effect was dose-dependent and did not occur with sub-hypnotic doses (Horsley, 1937). Thirty years later, these results were confirmed when either a thiopentone or pentobarbitone induction of anaesthesia was noted to be accompanied by a reduction of increased ICP in a small series of neurosurgical patients (Sondergard, 1961). In 1973, thiopentone was reported to reduce an increased ICP, while improving the overall CPP during induction of anaesthesia (Shapiro, Galindo and Wyte, 1973). This report clearly indicated that ICP reduction was not an event dependent upon reduction of arterial pressure, but resulted directly from an intracranial effect of the drug. The principle of inducing anaesthesia with a drug possessing potent cerebrovasoconstrictive properties was established, and thiopentone remains one of the most commonly used drugs for inducing anaesthesia in patients with intracranial hypertension. Use of barbiturates to control intraoperative episodes of increased ICP produced by noxious stimuli is generally accepted (Shapiro, 1975; Bedford et al., 1980). Barbiturates have also been used successfully as part of a multimodal therapy to control acute malignant intraoperative brain swelling (Day et al., 1982).

There have been several non-randomized clinical trials of high dose barbiturate therapy to reduce intracranial hypertension complicating craniocerebral trauma. The first clinical application of this approach was in 1974 and utilized a combination of coma-inducing doses of pentobarbitone and hypothermia to control persistently increased ICP (Shapiro, Wyte and Loser, 1974). Following this initial report, other clinical studies indicated that ICP control could be obtained without inducing hypothermia (Marshall, Smith and Shapiro, 1979b; Frost et al., 1981; Hoppe, Christensen and Christensen, 1981; Sidi et al., 1983). This decreased the logistical requirements for the therapy, and also improved the margin of safety by avoiding hypothermia-induced cardiac arrhythmias.

In comparing clinical experience with high-dose barbiturate therapy for ICP control in different institutions, several factors become clear. The first concerns the fact that this is a major undertaking requiring continuous intensive care support for days or weeks. A majority of the patients respond initially to barbiturate administration with reductions in ICP, often accompanied by increased CPP. However, ICP control may only be transient, and the relationship of barbiturate-related reductions in ICP to functional neurological outcome remains unclear.

Currently, a multicentre trial is in progress of high-dose barbiturate therapy for ICP control in head injured patients (L. F. Marshall, 1985, personal communication). The study has strict entry criteria which include: Glasgow Coma Score of 3–7, age 15–50 yr, a recent computerized tomographic brain scan, removal of operable haematoma, and failure of conventional aggressive therapy to control ICP (less than 25 mm Hg for 30 min, less than 30 mm Hg for 15 min, or less than 40 mm Hg for 1 min or longer). Conventional therapy for ICP control as defined in this study includes steroids, anticonvulsants, adequate sedation, muscle paralysis, recent administration of mannitol, Pa_{CO_2} less than 4 kPa (30 mm Hg), Pa_{O_2} greater than 9.3 kPa (70 mm Hg) and, when possible, drainage of CSF. Guidelines for the care of patients in this study include avoidance of hyperthermia and maintenance of cardiovascular stability, using a Swan–Ganz catheter to guide fluid and circulatory drug administration. Preliminary results describing the experience with the first 40 patients randomized into the study should have become available in late 1984.

High-dose barbiturate therapy has also been utilized for control of ICP in a variety of non-traumatic conditions associated with intracranial hypertension. These include near-drowning encephalopathy, Reye's syndrome and subarachnoid haemorrhage (Marshall et al., 1978; Belopavlovic and Buchthal, 1980; Conn et al., 1980; Woodcock, Ropper and Kennedy, 1982). No controlled studies exist in these situations, and although initial reduction in ICP may often be obtained in cases of non-traumatic intracranial hypertension, later in the course, increased ICP is often associated with brain death. This may be the case in this category of patient, because brain swelling is likely to be the result of neuronal death, rather than its cause (as is often the case in head trauma). Table II lists the indications and dose ranges for high-dose barbiturate therapy as applied in the intensive care unit.

TABLE II. *The use of barbiturate therapy in the ICU*

	Load ($mg\,kg^{-1}$)	Maintenance ($mg\,kg^{-1}\,min^{-1}$)	Range ($\mu g\,ml^{-1}$)	Indication	Author
Thiopentone	2	2	15	Sedation	Carlton, Karl and Goldiner (1978)
Thiopentone	—	2–4	54	Increased ICP	Lundar, Ganes and Lindegaard (1983)
Pentobarbitone	4–7	1–4	—	Increased ICP	Traeger and others (1983)
Pentobarbitone	15–35	0.5–1.3	20–40	Increased ICP	Schaible and others (1982)
Pentobarbitone	—	2–3.5	25–36	Increased ICP	Marshall and others (1978)

Technique of High Dose Barbiturate Therapy

Whilst not endorsing the general application of this therapy at the present time, the author recognizes that, in some individual and compelling clinical situations, barbiturates may be the only remaining therapeutic tool. This management outline is presented in the hope of improving patient safety as we await the results of studies which will clearly establish the indications and procedures for high-dose barbiturate therapy.

The following guidelines for the management of continuous high-dose barbiturate therapy for intracranial hypertension focus on the intensive care unit phase of therapy.

While directed mainly toward control of persistently increased ICP, these guidelines are applicable, with modifications, to patients with ischaemic cerebral vascular disease. In patients with severe intracranial hypertension, coma already exists and it may or may not be present in individuals with occlusive stroke. Patients with large cerebral hemisphere infarctions are prone to develop increased ICP as the terminal event (Ng and Nimmannita, 1970).

Side effects

Dose-dependent cardiovascular and ventilatory depression are the major side effects of large doses of barbiturates. In the ICU, the lungs of patients with increased ICP who are candidates for this treatment will already be mechanically ventilated. Much of the antecedent therapy reducing or preventing the development of intracranial hypertension involves diuretics and fluid restriction. This results in systemic dehydration and intravascular volume depletion. In this situation, the cardiovascular depressant effects of barbiturates are potentiated and severe hypotension with or without cardiac decompensation can occur (Shubin and Weil, 1965; Skovsted, Price and Price, 1970; Traeger et al., 1983). Barbiturates increase the capacitance of the venous bed by central and peripherial sympatholytic effects (Skovsted, Price and Price, 1970; MacKenzie, McGrath and Tetrault, 1976). In the absence of intravascular volume depletion, the direct cardiac effects of relatively high doses of barbiturates are minimal (Becker and Tonnesen, 1978; Chamberlain, Seed and Chung, 1977). Direct myocardial depression and, to a lesser extent, direct vasodilatation from barbiturates are likely to occur only when large bolus doses are administered rapidly (Altura and Altura, 1975; Chamberlain, Seed and Chung, 1977). These dangerous side effects can be obviated by slow administration of the loading dose and by adequate prior restoration of circulating blood volume. Fluid replacement should be accomplished with isotonic electrolyte or colloidal solutions under right atrial or pulmonary capillary wedge pressure monitoring (Traeger, et al., 1983) Rapid reductions in serum osmolality and overexpansion of vascular volume should be avoided, as they increase the propensity for development of cerebral oedema.

High doses of barbiturates interfere with thermoregulation and render the patients poikilothermic (Dominguez de Vilotta et al., 1981). Active warming or cooling may be required to maintain core temperature at 33–39 °C. As gastrointestinal motility is inhibited by high-dose barbiturate therapy, gastrointestinal feeding is contraindicated and nasogastric decompression required. Urinary output decreases in proportion to reductions in cardiac output and tubular reabsorption of glucose and sodium (Harvey, 1980). Barbiturates can increase hepatic microsomal activity, leading to alterations in biotransformation of barbiturates in addition to other drugs and hormones. While clinical experience indicates that infections complicating the management of prolonged coma are frequent, they are more likely to result from immobility and invasive monitoring than from a direct influence of barbiturates on bacterial clearance (Archer et al., 1981). Skilled nursing is a major requirement for the successful application of high-dose barbiturate therapy.

Monitoring

The selection of monitoring devices is based upon the need to assess direct cerebral effects of treatment, and to control deleterious cardiovascular–pulmonary side effects. Specialized monitoring for intracranial events related to the disease process or its response to treatment, or both, includes neurological examination, ICP measurement, EEG recording and, occasionally, computerized tomography (L. F. Marshall, 1985, personal communication).

Neurological examination during barbiturate coma is limited. Occasionally, deep tendon reflexes may be preserved, while brainstem signs (such as the oculo-cephalic and corneal reflexes and spontaneous ventilation) are abolished (L. F. Marshall, 1985, personal communication). Pupil size and configuratin remain useful determinants of brain deterioration even in the presence of high blood barbiturate concentrations. In this situation, they are usually constricted and non-reactive to light, but rapidly become dilated in response to brain herniation, hypoxia or reductions in CPP. Pupil alterations or abrupt persistent increases in ICP, or both, are indications for computerized tomography.

ICP monitoring is an absolute requirement for application of high-dose barbiturate therapy in head injured patients. It is probably also indicated when this therapy is applied to stroke patients, especially when the area of infarction is expected to be large. The preferred route for ICP monitoring is the ventricular catheter, as it provides a route for rapid volume decompression of the intracranial space. The subarachnoid bolt may be used when ventricular shift or collapse prevents easy access to the ventricular CSF space. ICP monitoring should be continued for 24–48 h following clearance of barbiturates from the blood after cessation of therapy.

Recording of EEG is a useful adjunct to monitoring high-dose barbiturate therapy in head injured patients. In stroke patients, continuous recording of the EEG is mandatory as it provides a major guide to barbiturate dose.

A number of investigators have questioned the validity of EEG monitoring (Kassell et al., 1980; Selman et al., 1981a). When ICP is high, cerebrovascular and cerebral blood volume responses to barbiturates may be unpredictable and bear little relationship to the EEG effect of the drug. Also, when the EEG is already abnormal or severely depressed, its effectiveness in determining the optimal dose of barbiturates may be questioned. In most instances of occlusive stroke, the opposite hemisphere EEG is usually intact and useful for guiding therapy. In certain situations where EEG activity is isoelectric, either from barbiturates or the disease process, measurement of auditory evoked potentials may be helpful. This measurement is useful in determining brainstem viability (Starr, 1976; Lundar, Ganes and Lindegaard, 1983). This type of monitoring of certain brainstem functions is possible because the auditory response potentials are resistant to very high doses of barbiturates (Prior, 1985).

During the loading and acute maintenance phase of barbiturate therapy, the (weight) pre-determined dose, rate of administration, and blood concentrations correlate poorly with the cerebral metabolic and haemodynamic responses (Kassell et al., 1980; Selman et al., 1981a). In this situation, the EEG correlates best with the CBF and CMR changes until the EEG plateaus at an isoelectric or burst suppression pattern. In the more chronic phases of maintenance of barbiturate coma, there is evidence to suggest that the relatively coupled relationship of the EEG to CBF and CMR may be broken (Gronert et al., 1981). This may be a manifestation of development of cerebral metabolic tolerance to barbiturates.

Continuous measurement of systemic arterial pressure is required when high dose barbiturate therapy is used. Since arterial and cerebral perfusion pressures are important determinants of barbiturate dosing, continuous monitoring of arterial pressure is required during induced barbiturate coma. The arterial catheter also provides access for obtaining arterial blood for determination of blood-gas status. A Swan–Ganz catheter completes the required invasive monitoring and is extremely useful in guiding replacement of fluid and the use of vasopressors. More generalized requirements include an i.v. cannula, nasogastric tube, ECG monitor, temperature determination, urinary bladder catheter and access to a laboratory which can rapidly perform blood barbiturate concentration determinations on a daily basis.

Induction and maintenance of high dose barbiturate therapy

In the ICU, pentobarbitone is the most widely used barbiturate for control of ICP and reduction of infarct size. Pharmacokinetic factors favouring the rapid central nervous system uptake and redistribution of thiopentone are unimportant when therapy is applied for several days. Pentobarbitone is associated with a more gradual onset of cardiovascular side effects and may therefore be safer. While no strict guidelines have been developed for induction and maintenance of high-dose barbiturate therapy, there is general agreement with regard to disease-specific therapeutic objectives. With intracranial hypertension the objective is reduced ICP with increased CPP. In focal cerebrovascular disease, the objective is induction of an EEG burst-suppression or isoelectric pattern and prevention of an ICP increase. These objectives should be achieved with minimal reduction in arterial systemic pressure.

The multicentre barbiturate trial for head injured patients can be used to provide reasonable guidelines for high dose barbiturate therapy (L. F. Marshall, 1985, personal communication). The initial portion of the loading dose of pentobarbitone is 10 mg kg^{-1} administered over 30 min with administration rate determined by the cardiovascular response. The objective is to maintain a mean arterial pressure in excess of 70 mm Hg, and cardiac filling pressures sufficient to maintain a cardiac index of 2 litre min^{-1} m^{-2}. Following this, pentobarbitone 5 mg kg^{-1} is given each hour for the next 3 h. Over the first 4 h of treatment, 20–25 mg kg^{-1} may be administered and this should result in a blood barbiturate concentration of greater than 2.0 mg dl^{-1}. A maintenance dose of 2.5 mg kg^{-1} h^{-1} should be given to achieve a stable blood barbiturate concentration of 3–4 mg dl^{-1}, and pentobarbitone concentrations should be determined at 4, 12 and 24 h after initiating therapy. If ICP control or EEG burst suppression, or both, are achieved before achieving the higher stable blood barbiturate concentrations, dosage is reduced accordingly. If hypotension below 70 mm Hg or a reduction in CPP below 50 mm Hg, or both, ensues, volume expansion or dopamine, or both, may be used to correct these conditions.

Following achievement of stable pentobarbitone concentrations and the desired therapeutic effect, blood barbiturate concentrations should be monitored daily with appropriate intensive care support (which includes continuing anticonvulsants—usually phenytoin). If escape of the ICP to values exceeding 20 mm Hg occurs and the barbiturate concentration is less than 3.0 mg dl^{-1}, additional pentobarbitone 5 mg kg^{-1} doses may be used to regain control of ICP. When ICP has been maintained at less than 20 mm Hg for 48 h, or the therapy period for stroke has elapsed (96 or more h), gradual reduction in therapy over 2–4 days may be attempted. Standard measures to control ICP intermittently, for example hyperventilation or osmotic diuretics, may be required during the tapering phase.

High blood barbiturate concentrations preclude determination of cerebral death using EEG methods. Cerebral death can be presumed when the ICP and arterial pressure are equal and no intracranial blood flow can be demonstrated with angiographic techniques.

SUMMARY

This review has indicated that barbiturates are useful in controlling ICP during anaesthesia in patients with intracranial hypertension. While laboratory data indicate that intraoperative administration of barbiturates during episodes of transient cerebral ischaemia, associated with surgical revascularization procedures, should be efficacious, current intraoperative results claiming benefit are anecdotal. Continuous high-dose barbiturate therapy (induced barbiturate coma) for occlusive stroke and persistently increased intracranial pressure is currently undergoing clinical trials. While it is clear that this therapy can often reduce increased ICP in head injured patients, its influence on neurological outcome remains to be determined by a multicentre trial at present in progress. Despite evidence that high-dose barbiturate therapy can reduce the area of infarction in occlusive stroke in the laboratory, organized clinical trials have not yet commenced.

Until more definitive knowledge is available concerning the influence of high-dose barbiturate therapy in treating different forms of cerebral ischaemia, its application should be viewed sceptically and limited to centres willing to create an organized data base for inter-institutional evaluation of this form of treatment. If barbiturate therapy proves successful and the mechanisms involved are better understood, drugs with fewer side-effects and risks may become available to combat cerebral ischaemia.

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DRUG THERAPY IN BRAIN ISCHAEMIA

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After many years of research, drug treatment in cerebral hypoxia is still controversial and no treatment appears to be firmly established. Not even the mechanisms causing damage have been established (Siesjö, 1981), only that they are linked to a disturbance in the oxygen demand: supply ratio.

Enthusiasm for new modes of therapy have waxed and waned. We have witnessed alternating enthusiasm for cerebral vasodilators, cerebral vasoconstrictors, cerebral metabolic depressants, free radical scavengers, membrane stabilizers, calcium blockers, drugs that improve blood rheology, and drugs that are reported simply to improve cerebral function in a "black box" fashion.

Part of the apparent conflicts in the literature may result from great variety in the models used to test pharmacological brain protection. To clarify some of the confusion it is important to differentiate between species, pre- and post-treatment and the main categories of cerebral hypoxia (table I).

TABLE I. *Categories of cerebral hypoxia*

- Global cerebral hypoxia
  - hypoxaemia
  - incomplete ischaemia
- Regional cerebral hypoxia
  - incomplete ischaemia
- Global cerebral anoxia
  - complete ischaemia

In global cerebral hypoxia, "global" pertains to the whole brain. This may result from hypoxaemia or incomplete ischaemia such as occurs with arterial hypotension or increased intracranial pressure. The second category comprises regional cerebral ischaemia, which always appears to be incomplete with some collateral circulation remaining.

The third category is cerebral anoxia or complete cerebral ischaemia, such as occurs following cardiac arrest.

The pathophysiology of these different types of hypoxia may vary greatly and thus a drug cannot necessarily be expected to have the same protective effect in all categories. As an example, some of the anaesthetic agents apparently reduce cerebral oxygen consumption ($CMRO_2$) by reducing electrical activity of the brain as witnessed on the EEG (Michenfelder, 1974; Newberg, Milde and Michenfelder, 1983). This mechanism can therefore be expected to be protective only when there is electrical activity present that may be reduced. This would not be the case during complete cerebral ischaemia where the EEG becomes isoelectric within seconds (Steen, Milde and Michenfelder, 1978). However, this does not preclude a protective effect by some other mechanism.

Similarly, a drug that works by reducing increased intracranial pressure (ICP) can obviously act only in models where ICP is increased and in many types of ischaemia the magnitude and importance of oedema/ICP is still unclear (e.g. in global, complete ischaemia). A drug which vasoconstricts in normal parts of brain should shunt blood from normal to ischaemic parts (reverse steal or Robin Hood phenomenon) and this may occur in regional ischaemia such as stroke, but not in situations where the whole brain is hypoxic.

If the possible mechanism of action of different drugs is correlated with the types of hypoxia in this way, some of the apparent conflicts in the literature may become explicable. Other factors, including age, temperature, haematocrit and blood-sugar con-

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centration should also be considered; not all studies are well-controlled in these respects.

A growing problem in studying literature in brain hypoxia is the vast number of books and journal supplements comprising manuscripts from a great number of symposia. Some of these secondary papers are good reviews of current literature, but many present results from investigations that have not passed peer review as original articles in a journal. One should be as careful in using these results and conclusions as in accepting abstracts as references. Many may prove valid, while others may not. One should also distinguish between reports from a drug manufacturer and from independent laboratories. Confirmation of results reported by the former should be required.

To guide the readers, in the reference list following this article, manuscripts from symposia are marked *, reports from the manufacturers †.

In this review, we discuss some drugs according to the classification and order noted in table II.

TABLE II. *Drugs which have been used in cerebral ischaemia*

1. Calcium entry blockers
2. Anticonvulsants and drugs depressing cerebral metabolism:
   Barbiturates
   Etomidate
   Midazolam
   Althesin
   Gammahydroxybutyrate
   Isoflurane
   Phenytoin
3. Drugs promoting microcirculation post-ischaemia:
   Vasopressors
   Heparin, Streptokinase
   Dextran 40, Fluosol DA
4. Prostaglandins and drugs affecting prostaglandin synthesis:
   Prostacyclin (PGI-2)
   Indomethacin
5. Free radical scavengers
6. Miscellaneous drugs.
   Corticosteroids
   Naloxone
   Dimethyl sulphoxide (DMSO)
   Piracetam

CALCIUM ENTRY BLOCKERS

Disturbed Ca^{2+} homeostasis resulting in increased intracellular Ca^{2+} concentrations has been incriminated during the past few years as a major trigger of tissue damage occurring during hypoxia (Siesjö, 1981; Raichle, 1983; White et al., 1983a) (see also Meldrum (1985)). Thus, the calcium entry blockers are currently being investigated for their potential protective effects against hypoxic damage.

Interest was originally focused on cardiac use. The first drug reported to have a calcium entry blocking effect, verapamil (Fleckenstein, 1964), has been used for treating cardiac arrhythmia for more than a decade, and there are now extensive reports that the calcium entry blockers can protect the myocardium against hypoxic damage (Braunwald, 1982; Landmark and Refsum, 1983). In the heart, these drugs have many effects—improving coronary blood flow and reducing the myocardial oxygen demand both by reducing afterload and by a negative inotropic effect (Landmark and Refsum, 1983). In addition, these drugs may have a direct protective effect on cells (Braunwald, 1982).

A reduction in oxygen consumption does not seem to occur in brain (Harper, Craigen and Kazda, 1981), although the other actions may be important. Cerebral hypoxia thus reduces extracellular calcium in brain (Nicholson, 1980; Harris et al., 1981), presumably by cellular uptake. CBF may then be reduced by:

(1) *Cerebral vasoconstriction* from an increased calcium concentration in vascular smooth muscle (Somlyo and Somlyo, 1968; Van Neuten and Vanhoutte, 1980; Vanhoutte, 1981).

(2) *Disturbed blood rheology*. Blood viscosity may increase by decreased deformability of red blood cells secondary to accumulation of calcium in the cell membrane (De Cree et al., 1979), and calcium may have an effect on platelet aggregation (Vanhoutte and Van Neuten, 1980).

It also appears that increase in the free cytosolic calcium in brain cells activates many catabolic reactions with breakdown of proteins and phospholipids (Schlaepfer and Bunge, 1977; Schaune et al., 1979; Farber, Chien and Mittnacht, 1981). The latter causes release of free fatty acids, including arachidonic acid with production of ecosanoids such as prostaglandins and thromboxanes, factors that may induce further tissue damage by further vasoconstriction, platelet aggregation etc., depending on the "balance" between the various substances (reviews Farber, Chien and Mittnacht, 1981; Siesjö, 1981; Raichle, 1983).

Large concentrations of calcium may also uncouple mitochondrial oxidative phosphorylation during hypoxia so that the oxygen supplied is used for pumping calcium into the mitochondria directly instead of being used for ATP production (Siesjö, 1981).

There is now a rapidly growing family of drugs that may block these effects, at least *in vitro*. They include verapamil, D-600, diltiazem, nifedipine, nicardipine, nimodipine, prenylamine, terodiline, fendiline, perhexiline, caroverine, flunarizine, cinnarizine and lidoflazine. In contract to cations such as manganese, cobalt and lanthanium which are non-selective competitive Ca^{2+} antagonists, these drugs act in nanomolar concentrations and exhibit stereospecificity, indicating a tight binding to specific structures (Braunwald, 1982). On the other hand, the diversity of molecular structure of these blockers indicates potentially different modes and sites of action.

Two types of study with calcium entry blockers may be distinguished. Some are concerned with one of the possible mechanisms for hypoxic damage such as vasoconstriction (spasm) or disturbed mitochondrial function, and thereby examine only some element(s) of the hypoxic situation. Others are concerned with the whole clinical entity of cerebral hypoxia and examine the eventual outcome.

In the first category are studies reporting dilatation of cerebral vessels, and this appears to be more effective than for other peripheral vessels as described for verapamil, diltiazem and nifedipine (Allen and Banghart, 1979; Shimizu, Ohta and Toda, 1980), nicardipine (Yamamoto, Otha and Toda, 1983) and nimodipine (Towart et al., 1982) after constriction caused by a variety of agents such as prostaglandins, serotonin, histamine, thromboxanes and blood constituents *in vitro*. There are indications that this tissue specificity may result from cerebrovascular muscle tone being more dependent on entry of extracellular calcium than on tone in other peripheral vessels (Allen and Banghart, 1979). Perhexiline, diltiazem and nifedipine failed to influenze CBF in normal rats (Edvinsson et al., 1983). It is hypothesized that these calcium entry blockers do not affect normal cerebral vasculature protected by an intact blood–brain barrier.

It is thus of interest to note that, although nimodipine *in vivo* has been reported to dilate human pial arteries (Auer, Oberbauer and Schalk, 1983) and increase non-ischaemic CBF in dogs (Kazda et al., 1982a), the effect in primates was significantly greater if the blood–brain barrier was disrupted osmotically before drug infusion (Harper, Craigen and Kazda, 1981). An increase in CBF for open- but not closed-skull primates was found by Harris and others (1982).

Calcium-induced stiffness of the red blood cells (RBC) may possibly be reduced by flunarizine and cinnarizine (De Cree et al., 1979; Van Neuten and Vanhoutte, 1980). Parker (1981) found no effect with verapamil and claims that the role of calcium in RBC deformability in hypoxia *in vivo* is not clear. We have previously studied pentoxifyllin (Steen, Milde and Michenfelder, 1982), a diesterase inhibitor supposed specifically to improve RBC deformability in hypoxia (Ehrly, 1978), and found no effect on CBF during MCA occlusion in cats.

There might be increased platelet aggregation in the brain during hypoxia (Aragno and Doni, 1976; Hossmann, Hossmann and Takagi, 1980). The importance of this or the modulating effects of calcium entry blockers are not clearly established, but a reduction in platelet aggregation factor release from human leucocytes has been described for nifedipine (Jouvin-Marche et al., 1983).

A protective effect of the calcium entry blockers directly on brain cells has not yet been established. Harris and others (1981) reported a decrease in extracellular Ca^{2+} with nimodipine compared with placebo during MCA occlusion in cats, indicating an increased cellular uptake (see below).

Whilst these effects may be important, the main question for the clinician is: how do calcium blockers affect the clinical outcome after cerebral hypoxia?

There are many reports of improved outcome in rodents exposed to a variety of insults (Hoffmeister et al., 1982; Karasawa et al., 1982; Kazda et al., 1982b; Van Reempts et al., 1983; Wauquier et al., 1983), but as most of the models are not clinically relevant and the studies are performed mostly in the manufacturers' laboratories, they serve only as screening investigations.

One study which may be clinically relevant was undertaken with MCA occlusion in rats (Mohamed et al., 1983), in which nimodipine significantly improved CBF in the ipsilateral auditory and parietal cortex with no effects on other parts of the brain. This indicated improvement in the periphery of a focal ischaemic lesion (the penumbra) with no adverse steal effect on the central core of ischaemia (frontal cortex, caudate nucleus).

To our knowledge there are no reports yet on the effect of calcium entry blockers in global cerebral hypoxia in larger animals, although in regional cerebral ischaemia there are several reports on cerebral blood flow, rather than outcome.

Nimodipine increased CBF by curtailing autoregulation during hypertension in primates both before and after cerebral arterial spasm had been induced by successive injections of blood to the basal cistern (Svendgaard et al., 1983). As CBF was measured by a xenon-133 technique, it cannot be concluded that nimodipine necessarily affected spasm. A "look-through" phenomenon may occur where the counter recording CBF in an area affected by spasm picks up an increase in CBF in a non-ischaemic area behind (Hanson, Anderson and Sundt, 1975). Nifedipine was found (by angiography) to reverse cerebral arterial spasm produced in dogs by blood injected to the cisterna 48 h apart (Allen and Bahr, 1979). Varsos and colleagues (1983) failed to confirm this.

In a prospective, double-blind, randomized study Allen and others (1983) reported fewer neurological deficits produced by vasospasm (verified on angiograms) with nimodipine than with placebo in patients with intracranial aneurysms. Fifty-six patients were treated with oral nimodipine for 21 days, commencing within 96 h of subarachnoid haemorrhage, compared with 60 placebo-treated controls. After 21 days, death or severe neurological deficit from arterial spasm occurred in significantly fewer of the nimodipine- than the placebo-treated patients: one of 56 compared with eight of 60. If all deficits attributed to spasm were included, including mild to moderate degrees (four nimodipine *v.* two placebo-treated), the difference was not significant. There was, furthermore, no difference in the degree of spasm for patients with normal outcome.

Even in this multicentre study, the total number of patients with deficits attributed to spasm is small, and a recent editorial (Editorial, 1983) suggested that the data presented did not justify the assertion that the clinical efficacy was a result of inhibition of spasm. On the other hand, CAT scans indicated that a larger amount of subarachnoid blood before start of treatment was associated with a worse outcome in the placebo group, but not in the nimodipine group (Allen et al., 1983) and this would link the effect to reduction in spasm, as there appears to be a close relationship between subarachnoid blood and spasm.

In an uncontrolled study (Auer et al., 1982) of 17 patients operated for ruptured aneurysm 48–72 h after subarachnoid haemorrhage, topically applied nimodipine produced vasodilatation. After operation, topical application through a cannula placed during the operation was reported to reverse spasm in one of two patients and cause vasodilatation in five of seven patients without spasm.

We conclude that the calcium entry blockers, at least nimodipine, seem to be promising therapeutic agents in regional ischaemia from spasm, but more studies are required to confirm the original reports.

The efficacy of calcium entry blockers in other focal ischaemic events is less well established. Verapamil had no effect on ischaemic CBF, blood-brain barrier breakdown or other pathological changes during MCA occlusion in cats (Reedy et al., 1983). On the other hand, nimodipine increased ischaemic CBF during MCA occlusion in primates (Harris et al., 1982), but at the same time nimodipine-treated monkeys required higher CBF values to avoid the development of cortical oedema and a disturbed ion homeostasis than did control monkeys. Although nimodipine greatly improved ischaemic blood flow, this effect obviated other deleterious effects of the drug. Topical application of nimodipine also produced vasodilatation of cortical arterioles contracted after MCA occlusion in cats (Harris et al., 1982; Brandt et al., 1983; Reedy et al., 1983), but none of these studies reported on the eventual outcome of the animals.

Nemoto and others (1983) and Kaneko and colleagues (1983) have reported reductions in increased ICP with nifedipine or D-600 after a cortical freeze injury in cats. Reduction of oedema and ICP may be related to a more rapid recovery of cellular function. For D-600 (Kaneko et al., 1983) there was no difference in oedema formation or blood–brain barrier breakdown, and, as the calcium entry blockers should not reduce ICP by vasoconstriction, these results lack adequate explanation. However, they do fit with a report on cortical freeze injury in rats. Heller and others (1983) found an increase in local CBF in the area 24 h after injury and nimodipine did indeed decrease this high CBF.

When flow has been re-established after a period of complete cerebral ischaemia, a transient 5–15 min period of increased CBF is followed usually by a period of prolonged hypoperfusion with CBF down to 20–30% of control despite normal arterial pressure (Hossmann, Lechtape-Grüter and Hossmann, 1973; Steen et al., 1983a) It has been suggested that the magnitude of the neurological damage results in part from this delayed hypoperfusion (Siesjö, 1978; White et al., 1983a) and that increased calcium concentrations intracellularly might be responsible for this (Kazda et al., 1982a; White et al., 1983a). The effect of calcium blockers on this hypoperfusion has therefore been examined.

Flunarizine (White et al., 1982), lidoflazine, verapamil and magnesium sulphate (White et al., 1983b) appeared to abolish hypoperfusion in dogs when given after 20 min of complete cerebral ischaemia obtained by ventricular fibrillation with reflow established by cardiopulmonary bypass. Some uncertainty applies to these results as the control CBF values (mean 200–250 ml min^{-1}/100 mg) were two to three times that reported normally for dogs and validation of their thermal method used for CBF measurements is, to our knowledge, not yet published. In other studies flunarizine (Newberg et al., 1984) and lidoflazine (Dean et al., 1983) failed to influence the hypoperfusion period in dogs.

Nimodipine improved CBF in the hypoperfusion period in cats (Kazda et al., 1982a) and in dogs, both when treatment was commenced before (Steen et al., 1983a) and after ischaemia (Steen, Newberg et al., 1984). None of these studies reported on regional distribution of CBF however, and Smith and colleagues (1983) found that, although global CBF post-ischaemia was improved by nimodipine, there were great regional differences in rat brains, with a picture much like that obtained by hypercapnia in the same model. Smith and colleagues (1983) studied return of blood flow after 15 min of severe incomplete ischaemia and, although unlikely, a difference from the delayed hypoperfusion after complete ischaemia cannot be excluded. Whatever are the effects on CBF, neurological outcome is again the important issue.

In a controlled blind study (Winegar et al., 1983) lidoflazine was given as part of the resuscitation after 15 min of cardiac arrest obtained by potassium injection in dogs. This study indicated that lidoflazine might improve the neurological recovery in that all five treated dogs had spontaneous ventilation, reactive pupils, voluntary movements and response to tactile stimuli 12 h after resuscitation, while four of five controlled dogs had maximum neurological deficit scores. Lidoflazine also appeared to improve the outcome when given after 10 min ventricular fibrillation in dogs, but not after 7 or 10 min of asphyxial cardiac arrest (Vaagenes et al., 1983).

Flunarizine did not improve the outcome in dogs 48 h after ischaemia when it was given after 10 min of complete cerebral ischaemia obtained by cross-clamping the aorta (Newberg et al., 1984). In contrast, nimodipine commenced before ischaemia significantly improved the outcome 48 h after ischaemia (Steen et al., 1983a). When nimodipine was commenced after ischaemia, the neurological outcome was intermediate, not significantly different from either control or pretreated dogs (Steen, Newberg et al., 1984).

In a recent, controlled, blind primate study from Michenfelder's laboratory (Steen, Gisvold et al., 1984) nimodipine treatment was commenced 5 min after 17 min of complete cerebral ischaemia obtained by a neck-cuff inflated to 1500 mm Hg combined with arterial hypotension to 50 mm Hg. Completeness of ischaemia was confirmed by a xenon-133 technique. The monkeys were given intensive care for 96 h, followed by neurological and pathological evaluation, and nimodipine significantly improved the outcome.

Thus, both lidoflazine and nimodipine may improve the outcome in models of complete cerebral ischaemia such as occurs with cardiac arrest. No human studies have been reported yet, but an international multicentre study is currently being launched.

Finally, there is one group of double-blind studies reporting on the effects of flunarizine on chronic cerebral dysfunction in geriatric patients (Staessen, 1977; Lehrl, Sollberg and Schumacher, 1978; Nelson et al., 1978; Zissis, Alevizas and Dontas, 1981). The criteria for patient selection are not well described in any of the studies, and in one (Nelson et al., 1978), more than 100 doctors were involved in the trial. All studies reported improvements in some cerebral function or symptom, compared with placebo, but often not the same effect and there was usually also a significant placebo effect.

There is no good explanation to account for improvement in the patients. It may be hypothesized that, in these brains with diffuse cerebrovascular disease, the drugs improved blood supply to parts which normally receive sufficient only to survive, but not enough for normal function. The existence of such areas has never been established, and with the great placebo-effects reported also in these studies, results should be interpreted with great caution.

We conclude that, at present, calcium entry blockers seem promising for treatment of patients with regional cerebral ischaemia, at least when this results from vasospasm such as in subarachnoid haemorrhage, and in treatment of patients with complete cerebral ischaemia such as occurs in cardiac arrest. In the former category, more human studies are needed, whilst in the latter, no human reports are available yet.

ANTICONVULSANTS AND DRUGS DEPRESSING CEREBRAL METABOLISM

Various agents which depress cerebral metabolism have been investigated to examine the hypothesis that, in situations with limited oxygen supply, depression of cerebral oxygen demand may produce improved balance between oxygen supply and demand, thereby preventing detrimental metabolic effects.

Of these drugs, the most extensively investigated are the barbiturates, which are considered separately in this issue (Shapiro, 1985). Other drugs include etomidate, gammahydroxybutyric acid, Althesin, midazolam and isoflurane.

The most effective procedure for metabolic inhibition is probably hypothermia, which may enable the brain to tolerate prolonged periods of circulatory arrest. It is worth mentioning that the mechanism by which hypothermia depresses metabolism is probably different from that by drugs. Hypothermia appears to cause general depression of cerebral metabolism, whereas the barbiturates (and possibly also other drugs) depress only that part of metabolism related to active electric function (Michenfelder, 1974). Thus, barbiturates have no apparent metabolic effects when the EEG is isoelectric (Steen et al., 1983b). If this hypothesis is correct, hypothermia should be superior to drug-induced depression of cerebral metabolism in maintaining cellular viability during periods of limited oxygen supply. This appears to occur during short hypoxic episodes, while long-term hypothermia (48 h) has been reported to cause circulatory disturbances (Steen, Soule and Michenfelder, 1979).

Etomidate

Etomidate is a short-acting hypnotic with greater cardiovascular stability than barbiturates. It is a potent depressant of $CMRO_2$, possesses anticonvulsant properties, is a cerebral vasoconstrictor and can thus reduce an increased intracranial pressure both in animals and man (Moss et al., 1979; Wauquier, 1983). Etomidate has been investigated extensively in rodents with various brain ischaemic insults (Wauquier, 1983). As with the calcium entry blockers, the studies are mostly reported by drug manufacturers, are not directly clinically relevant and lack long-term evaluation of neurological function. Therefore they serve only as screening investigations.

To our knowledge, no well controlled studies have been performed evaluating the long-term neurological effects of etomidate.

Midazolam maleate

Midazolam is a water soluble benzodiazepine reported to have a shorter duration of action than diazepam, and with little action on the cardiovascular system. Midazolam greatly reduces $CMRO_2$ in dogs without severe haemodynamic depression (Nugent, Artru and Michenfelder, 1982).

We are unaware of any study of clinically relevant regional or global ischaemia with long-term neurological evaluation.

Althesin

Althesin is a rapidly acting, rapidly excreted i.v. agent, with anticonvulsant properties, which decreases $CMRO_2$ and CBF (Sari et al., 1978) and can thus also decrease increased intracranial pressure (Turner et al., 1973). It is therefore possible that this agent may be evaluated for brain protective effects.

Gammahydroxybutyrate (GHB)

Gammahydroxybutyrate is a naturally occurring inhibitory neurotransmitter and may be administered as gammabutyrolactone (GBL), which is hydrolysed by a lactonase present in blood and liver but not in brain. GBL can reduce the rate of glucose utilization in the rat brain to the same extent as the barbiturates (Wolfson, Sakurada and Sokoloff, 1977), but GBL/GBH offered only modest prolongation of survival in hypoxaemic mice, in spite of the fact that it has a strong depressant effect on $CMRO_2$ (Artru, Steen and Michenfelder, 1980). A possible limiting factor is that CBF seems to be reduced more than $CMRO_2$, and since there also is a reduction in cardiac output, this may create an unfavourable imbalance between oxygen supply and demand in the brain. In contrast, GBL significantly reduced neuronal tissue loss during experimental forebrain ischaemia in the awake rat (Lavyne et al., 1983). Furthermore, low dose GBL prevented both the early hyperaemia usually seen in non-treated controls during reperfusion after ischaemia, and the prolonged delayed post-ischaemic hypoperfusion (Lavyne et al., 1983).

A protective effect may be explicable if GBL directly inhibits glucose utilization and thus possibly reduces the formation of lactic acid during hypoxia. The same authors claim that GHB may produce seizures in experimental animals, however, and they advocate caution in neurosurgical situations.

Isoflurane

Isoflurane possesses some properties not common to the other volatile anaesthetics. It may produce an isoelectric EEG at concentrations that are haemodynamically well tolerated (approximately 2 MAC) and $CMRO_2$ is reduced gradually with increasing concentration, down to approximately 50% of control when the EEG becomes isoelecric, with no further effects in higher concentrations (Newberg, Milde and Michenfelder, 1983). This differs from halothane, with which approximately 4.5% (5 MAC) is required to achieve an isoelectric EEG, a concentration not tolerated haemodynamically without cardiovascular support. Furthermore, $CMRO_2$ continues to decrease with higher concentrations of halothane in the face of an isoelectric EEG. More than 2% halothane causes disturbances in the cerebral energy state and an increase in lactate concentration and lactate:pyruvate ratio, indicating a toxic effect, possibly by interfering with oxidative phosphorylation (Michenfelder and Theye, 1975). Isoflurane has therefore an effect on cerebral metabolism qualitatively different from that of halothane, and it has been reported to improve the cerebral energy state in dogs during incomplete global ischaemia to the same degree as barbiturates when compared with controls (Newberg and Michenfelder, 1983).

Although it may appear that any agent depressing cerebral metabolic rate is a potential cerebral protective agent, this is not so. Although reducing $CMRO_2$, halothane is harmful in regional cerebral ischaemia (Smith et al., 1974). This might result from other potentially detrimental effects, including vasodilatation, with halothane overriding a potentially protective effect. Furthermore, as noted above, the reduction in $CMRO_2$ with high concentrations of halothane appears to indicate a toxic effect with disturbances in oxidative phosphorylation. In addition, in rats there was no apparent protective effect during severe incomplete ischaemia with chlormethiazole (Carlsson and Rehncrona, 1979), a potent depressor of cerebral metabolism, or with a combination of diazepam and nitrous oxide which depressed $CMRO_2$ to the same degree as barbiturates with less cardiovascular depression (Berntman et al., 1979). In these instance, the absence of a protective effect may result from lack of metabolic effects. As suggested above, if the ischaemia is severe enough to render the EEG isoelectric, these drugs probably have no effects on cerebral metabolism.

Phenytoin

Phenytoin was reported to improve neurological recovery and histopathology in global cerebral ischaemia produced with a pneumatic cuff in rabbits (Aldrete et al., 1979). In another study of post-ischaemic treatment, phenytoin also improved histopathology in comparison with placebo. Thiopentone produced intermediate results, not significantly different from either placebo or phenytoin (Cullen et al., 1979). These results should be interpreted with caution. Post-ischaemic care was not described in either study, and in the latter, no physiological variables or neurological outcome were reported and both the cerebral cortex and brainstem were excluded from the histopathological reports.

In an uncontrolled study (Aldrete et al., 1981) with phenytoin given after cardiac arrest which occurred during or after anaesthesia, nine of 10 patients recovered almost completely. Before treatment, the patients were comatose with dilated, areflexic pupils and abnormal posturing, As this was only a small, uncontrolled study in a patient group where a reasonably good result might be expected since the insult occurred in hospital, further studies are necessary before any conclusion may be drawn.

Phenytoin may protect the brain by various mechanisms. It has been reported to slow the release of potassium from ischaemic neurones, and this release may be an indication of ischaemic brain damage (Artru and Michenfelder, 1981). The effects of phenytoin on cerebral metabolism and blood flow are unclear. Brodie and Nelson (1968) reported that phenytoin reduced the high energy phosphate and glucose utilization rate by approximately 50% after decapitation in mice, while Artru and Michenfelder (1980) failed to find any effect on cerebral metabolism in the dog *in vivo*. It is possible that the anticonvulsant effect of phenytoin may contribute to a possible protective effect.

DRUGS PROMOTING MICROCIRCULATION

A no-reflow phenomenon, where parts of the brain cannot be reperfused after periods of complete cerebral ischaemia has received much attention (Ames, Wright and Kowada, 1968). Although others have failed to find this phenomenon after complete ischaemia lasting even 10 min or more (Marshall et al., 1975; Steen, Milde and Michenfelder, 1978), there is a pronounced reduction in overall post-ischaemic CBF despite adequate arterial pressure (delayed hypoperfusion discussed above), and it is possible that the blood flow pattern is uneven whether caused by red cell sludging, platelet aggregation, pericapillary oedema or vasospasm. Much interest has therefore focused on promoting the microcirculation after periods of complete cerebral ischaemia (see the discussion on calcium entry blockers above).

A rapid normalization of arterial pressure after ischaemia should be attempted, since post-ischaemia hypotension has been shown to cause additional brain damage (Cantu, Ames and DiGiaciento, 1969) and a post-ischaemic period of hypertension has been reported to improve reperfusion inhomogeneity (Fischer and Ames, 1972; Nemoto et al., 1979). It is not clear if transient hypertension with vasopressors should be induced; clinically, this concept is supported only by anecdotal reports (Wise, Sutter and Buckholder, 1972). Several investigators have explored further use of viscosity-reducing measures in order to improve post-ischaemic rheology. Heparin combined with hypertension and haemodilution given after cardiac arrest in dogs apparently improved outcome (Safar, Stezoski and Nemoto, 1976), as did heparin alone given immediately before or shortly after global cerebral ischaemia in cats (Stullken and Sokoll, 1976). In a model of multi-focal cerebral ischaemia in dogs, Hallenbeck and others (1982) found that prostacyclin and indomethacin improved neurological function after multifocal ischaemia in dogs, but only when combined with heparin. The combination of indomethacin and heparin given before ischaemia, or prostacyclin, indomethacin and heparin given after ischaemia also increased post-ischaemic CBF after complete cerebral ischaemia produced by spinal fluid compression in dogs (Hallenbeck and Furlow, 1979). Finally, streptokinase in combination with dextran 40 produced a more rapid return of EEG activity and higher cortical CBF after cardiac arrest in dogs than those receiving placebo or dextran 40 alone (Lin et al., 1978). Unfortunately, neurological outcome was not studied.

Recently, haemodilution using the oxygen-carrier fluosol DA has been reported to reduce infarct size and improve neurological outcome in a model of focal ischaemia (Peerless et al., 1981). Takagi and colleagues (1983) found that fluosol DA improved outcome after 30 min of severe, global ischaemia in rats when judged by restoration of EEG and histology. Sutherland and Farrar (1983) found that treatment with fluosol DA increased oxygen availability in the brain after ischaemia.

It should be noted that, although possible, there is no definite evidence that the hypoperfusion occurring after complete cerebral ischaemia is harmful to the brain, except in the case of a true no-reflow phenomenon. Attempting to improve the collateral circulation during regional ischaemia may be a more established indication for promoting the microcirculation.

PROSTAGLANDINS AND DRUGS AFFECTING PROSTAGLANDIN SYNTHESIS

The normal biosynthesis of prostaglandins, thromboxanes and leukotriens may be affected during and after ischaemia. These products are metabolites of arachidonic acid, and oxygen is necessary for normal synthesis. The enzyme cyclo-oxygenase catalyses the formation of prostaglandin intermediate PGG-2 from arachidonic acid in a reaction requiring oxygen. Once formed, PGG-2 is converted to other prostaglandins, of which some are vasoconstrictors while others vasodilate. It is interesting to note that active oxygen species (free radicals) are generated as normal byproducts. Prostacyclin (PGI-2) is a potent vasodilator which also prevents platelet aggregation.

Thromboxane (primarily thromboxane A_2) synthesis is also dependent on the enzyme cyclo-oxygenase. Thromboxane A_2 has an effect opposite to that of prostacyclin; it promotes platelet aggregation and vasoconstriction. Normally, a delicate balance exists between these two systems (for excellent reviews, see Raichle, 1983 and Siesjö, 1981).

The synthesis of both substances is reduced after pretreatment with indomethacin which is a cyclo-oxygenase inhibitor. Gaudet and Levine (1979) found that treatment with indomethacin before bilateral carotid occlusion not only inhibited the increase in prostacyclin and thromboxane, but the treated gerbils recovered more rapidly and were more active than controls.

The effects of prostacyclin (PGI-2) and indomethacin on post-ischaemic circulation and recovery have been studied in various types of ischaemia. As reported above, Hallenbeck and colleagues (1982) found that a combination of prostacyclin, indomethacin and heparin improved neurological function after multifocal ischaemia in dogs. In another study, pretreatment with indomethacin increased CBF after global ischaemia in rabbits and focal ischaemia in cats, but failed to influence the return of EEG activity (Boulu et al., 1982). Again, long-term neurological outcome or pathology was unfortunately not reported. In an interesting study in heparinized rabbits subjected to 20 min of complete cerebral ischaemia, a (synthetic polymeric prostaglandin given after ischaemia improved the neurological outcome when evaluated 24, 48 and 60 h after ischaemia (Kolata and Polis, 1980). At 24 h, seven of 10 recovered compared with three of 10 in the placebo-treated group. Recovery was strikingly rapid in the treated animals—very different from the controls. The mechanisms of action are not established, and CBF was not measured.

Pickard (1981) found that CBF was reduced by indomethacin under normal conditions, but increased during post-ischaemic recirculation. Thus it appears that, contrary to normal conditions, thromboxane synthesis is inhibited more strongly by indomethacin post-ischaemia than prostacyclin synthesis, thereby favouring prostacyclin.

Treatment with prostacyclin has been utilized also in patients with stroke (Gryglewski et al., 1983). The patients were treated with prostacyclin between 1 and 5 days after hospital admission and all had dramatic improvement in neurological function. As there was no control group, no clear conclusions can be drawn.

FREE RADICAL SCAVENGERS

It is still not clear which components of the complex post-ischaemic pathophysiology are the most important in causing neuronal destruction and death. The importance of calcium ions in addition to prostaglandins and other metabolities of arachidonic acid have been discussed above. Another possibly important component is an increased concentration of free radicals during or after ischaemia (Siesjö, 1981; Raichle, 1983).

A free radical is defined as any atom, group or molecule with one unpaired electron occupying an outer orbital. This implies a high energy state and thus renders the free radical highly reactive. They have the capacity to initiate destructive reactions in biological membranes and other cellular structures, and may be of central importance in causing further damage during or after ischaemia (Demopoulos, Flamm and Pietronigro, 1980). Hence, it has been suggested that treatment with so-called free radical scavengers (thiopentone, vitamin E, mannitol, DMSO, vitamin C and many other substances) may reduce or prevent further damage during this period. To our knowledge, there are no controlled experimental data on cerebral ischaemia (focal or global) indicating a therapeutic effect of free radical scavengers. It is interesting, however, that current research is focused on calcium, prostaglandin synthesis and free radicals. These represent different approaches to the same problem (free oxygen radicals are normal by-products of prostaglandin synthesis), and it is possible that the calcium ion holds a key position in this chain of reactions.

MISCELLANEOUS DRUGS

Corticosteroids

The value of corticosteroids is controversial in ischaemic cerebral insults and brain trauma. Most interest has focused on the effect on oedema formation and the reader is referred to the article by Klatzo (1985) in the present Symposium. Recent investigations in large series of patients seem to indicate that there is no difference in outcome between steroid-treated and other patients with severe head injury (Cooper et al., 1979). However, the evidence is controversial with respect to focal ischaemia. Prophylactic steroid therapy was found to decrease oedema and improve regional cerebral blood flow after middle cerebral artery occlusion in cats (Bartko et al., 1972); Others have failed to confirm this when dexamethasone was given after onset of ischaemia in cats (De la Torre and Surgeon, 1976) and either before or after onset of ischaemia in primates (Lee et al., 1974).

Fishman (1982) stated in a review article that there is no proof of beneficial effects of steroids on oedema associated with hypoxia (or ischaemia) or in head injury. However, he speculated that they may have a beneficial effect by inhibiting the release of arachidonic acid from cell membranes.

There are studies indicating that steroids may stabilize lyzosome membranes, prevent release of lytic enzymes and stabilize mitochondria and capillary walls. White, Hoehner and Wilson (1980) suggested that dexamethasone may improve ATP synthesis and partly protect the mitochondria from uncoupling. Marcy, O'Connor and Welsh (1981) demonstrated improved recovery of ATP synthesis with dexamethasone treatment when recirculation was re-established after 30 min of bilateral carotid artery occlusion in cats.

Naloxone

Several reports indicate that the opioid antagonist naloxone can improve neurological function in various types of cerebral insult. In two patients with focal cerebral ischaemia, naloxone completely reversed the neurological deficits, while morphine re-induced the hemiparesis in one (Baskin and Hosobushi, 1981). In gerbils with occlusion of one carotid artery, the level of immunoreactive beta-endorphin-like material was 40–80% higher in the ischaemic hemisphere than on the control side, and repeated administration of naloxone consistently reversed all neurological deficits. As the deficits tended to revert after 20–30 min, they implanted 10-mg pellets of naloxone subcutaneously, and this produced a sustained reversal of the neurological deficit (Hosobushi, Baskin and Woo, 1982). These studies suggest that endorphins may be involved in this type of ischaemia. However, there are also negative reports on the use of naloxone in focal ischaemia. Shigeno and others (1983) found no effect of naloxone on local cerebral glucose utilization when given after MCA-occlusion in rats, and Cap de Ville and colleagues (1983) found no effect on neurological function when it was given during or 60 min after 30 min of severe global ischaemia in rats (four vessel ischaemia).

We are not aware of any studies of naloxone in complete global ischaemia such as occurs in cardiac arrest.

Dimethyl sulphoxide (DMSO)

DMSO is a water soluble organic solvent used industrially since the 1940s. There are a substantial number of possible beneficial effects of DMSO. It has diuretic actions and has therefore been used in control of ICP after failure of other osmotic agents and barbiturates (Waller et al., 1979). It is a free radical scavenger, may improve post-ischaemic blood flow by vasodilatation, and rheology by an anticoagulant effect and reduced platelet adhesiveness and aggregation (Kligman, 1965). In MCA occlusion in Rhesus monkeys, DMSO significantly reduced the neurological deficits after ischaemia (De la Torre and Surgeon, 1976). In this study, DMSO had a strong diuretic effect, and caused a reduction in brain swelling after ischaemia. The latter was found also with dexamethasone treatment, but this did not affect the clinical outcome. De la Torre and Surgeon speculated that the most important effects of DMSO may be those on blood rheology, but so far a protective effect of DMSO has not been firmly established.

Piracetam

Piracetam was first reported to have possible brain protective effects in hypoxia by Giurgea, Mouravieff-Le-Suisse and Leemans in 1970. Richardson and Bereen (1977) reported a beneficial effect compared with placebo on the level of consciousness after neurosurgery, in a study including 106 patients with various intracranial lesions. The authors noted that piracetam is a cyclic derivative of gamma-aminobutyric acid, which is a neurotransmitter, and that the effect of piracetam may be linked to this effect. We are not aware of any published studies on piracetam in experimental focal or global brain ischaemia.

CONCLUSION

Many drugs have been suggested to protect the brain against hypoxic damage. Despite the huge investment of resources in this field, no accepted drug therapy has yet emerged. The only undisputed therapeutic principle is to improve the oxygen demand:supply ratio. A reduction in oxygen demand may be accomplished with drugs in some instances; an improvement in blood flow and oxygen supply has been suggested with others, but no controlled human studies with unequivocal results have emerged so far. When we have achieved greater understanding of the mechanisms of hypoxic damage, it will be possible to explore systematically potentially protective drugs, and we may then expect to make more rapid progress in this field.

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INDUCED HYPOTENSION AND BRAIN ISCHAEMIA

D. GORDON McDOWALL

Global or focal brain ischaemia may result from the technique of induced hypotension. In the presence of a normal cerebral circulation, ischaemia is of the global type and this situation is considered first.

GLOBAL ISCHAEMIA

Autoregulation

Autoregulation is the term used to describe the maintenance of constant perfusion over a range of arterial pressures. Autoregulation occurs in all vascular beds, but other mechanisms also act on vascular control, for example autonomic activity and plasma concentrations of hormones. The influence of these other mechanisms varies widely between different circuits, so that the effect of induced hypotension is different on the vascular systems of the brain, lung and kidney. For example, sudden blood loss causes more marked vasoconstriction in kidney than in myocardium. In brain, the influence of mechanisms other than autoregulation is relatively small. Thus, maximal sympathetic activity reduces CBF by only 20% (Harper et al., 1972) which is approximately the same as the change produced by a decrease of 1 kPa in arterial $P\text{CO}_2$. Autoregulation is therefore predominant in the cerebral circulation and acts to maintain CBF constant over a range of mean arterial pressures (MAP) which extend from 60 to 130 mm Hg in man (Lassen and Christensen, 1976). If, during induced hypotension, MAP is reduced beyond the lower limit of autoregulation, CBF starts to decrease in parallel with MAP until the ischaemic thresholds discussed by Symon (1985) and Heuser and Guggenberger (1985) are reached. It is important to note that the lower limit of autoregulation is that arterial pressure at which flow starts to decrease, and it has no significance itself in indicating brain ischaemia. There is a considerable margin of blood flow and arterial pressure between the lower limit of autoregulation and the ischaemic thresholds for EEG silence and failure of cell membranes. On the other hand, it is true that there can be no ischaemia until MAP has decreased below the lower limit of autoregulation.

The autoregulation curve as usually reproduced is, in a way, an abstraction. It relates aortic pressure to overall cerebral perfusion, but the important pressure for tissue perfusion is the perfusion pressure, which is the pressure gradient across the vascular bed—that is, for brain, MAP minus mean ICP, when the skull is closed. In normal physiological circumstances, the differences between MAP and perfusion pressure hardly matter, since ICP is normally low and decreases further with hypotension.

In the neurosurgical patient with haematoma or oedema, ICP becomes a major component in determining perfusion pressure and this must be borne in mind if arterial pressure is reduced during the early stages of a neurosurgical operation before the dura is opened. In some circumstances, for example head injuries, perfusion pressure may be inadequate entirely on account of an increased ICP in the presence of a normal, or even increased, arterial pressure (Miller, 1985). The other problem regarding the conventional autoregulation curve is that it relates to mean blood flow, whilst in situations of hypotension, blood flow becomes heterogenous and decreases more severely in some areas than others. The boundary zones between the territories of vascular supply are the sites of lowest perfusion (Adams, 1967). These territories lie between the distribution areas of the anterior, middle and posterior cerebral arteries and the superior and inferior cerebellar arteries. The reason for the vulnerability of

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these areas is that local arterial pressure is lower at these sites than elsewhere because of branching of the arterial tree. Consequently, a critically low perfusion pressure is reached in these areas at higher values of aortic pressure than in other parts of the brain. The concept of boundary zones is discussed fully in this Symposium (Graham, 1985).

It has been known for a number of years that the position of the autoregulation curve on the pressure–flow diagram depends to some degree on the method used to reduce arterial pressure. As a generalization, the worst case is hypotension resulting from blood loss, while drug-induced hypotension has lesser effects on cerebral perfusion (Fitch et al., 1976). The autoregulation curve in drug-induced hypotension is to the left of the autoregulation curve associated with haemorrhage and, in particular, the lower limit of autoregulation is at a low arterial pressure in drug-induced, compared with haemorrhagic, hypotension.

The reason for this is thought to be that blockade of sympathetic innervation of the pial arteries by drugs such as trimetaphan prevents the vasoconstriction which haemorrhage produces in these medium-sized vessels. As pointed out above, maximum sympathetic stimulation reduces CBF at normotension by not more than 20%. However, such small differences assume importance at low MAP (Harper et al., 1972). Furthermore, more recently it has become clear that there are differences in the autoregulation curve between different hypotensive drugs, with nitroprusside (NTP) being associated with the greatest leftward shift on the curve (Stoyka and Schutz, 1975; Michenfelder and Theye, 1977; Maekawa, McDowall and Okuda, 1979).

Autoregulation is often impaired in areas of brain pathology, for example around traumatic brain contusions, tumours and in areas of cerebral vasospasm (Palvogyi, 1969; Overgaard and Tweed, 1974; Enevoldsen and Jensen, 1978). In such cases, cerebral perfusion decreases with any reduction in arterial pressure and it has been suggested that critically low perfusion may occur at greater arterial pressures in the absence of autoregulation. The present author believes that this is only true if local tissue pressure is high as a result of oedema.

Changes in brain surface P_{O_2} *and electrical activity*

The pattern of P_{O_2} on the surface of the cerebral cortex is moved to lower P_{O_2} values during hypotension and this effect is more severe during trimetaphan (TMP) than NTP hypotension, whilst haemorrhagic hypotension produces the worst P_{O_2} profile (Maekawa, McDowall and Okuda, 1979). However, it is difficult to define ischaemia on the basis of tissue P_{O_2} measurement, because some neurones normally exist in an environmental P_{O_2} of approximately 0.3 kPa. A more direct approach is obtained by looking for derangements in brain function.

As Prior (1985) describes elsewhere in this Symposium, one of the derangements of function produced by ischaemia is suppression of cortical electrical activity. It has been demonstrated that electrical activity, as measured by the cerebral function monitor (CFM), is depressed at greater values of MAP during TMP compared with NTP hypotension (Ishikawa and McDowall, 1981; Prior, 1985). This would suggest that ischaemic thresholds are indeed different between these two hypotensive drugs, the advantage being with NTP. Of course, suppression of electrical activity, although indicative of an ischaemic depression of function, should not be equated with structural damage to the brain. It is well established that the brain can recover from ischaemia sufficiently severe to cause isoelectric EEG. Indeed, in a retrospective analysis of intraoperative CFM recordings during cardiopulmonary bypass, Malone, Prior and Scholtz (1981) showed that the CFM had been isoelectric for more than 7 min in all patients who later died with histological ischaemic brain damage. The clinical message would appear to be that if, during drug-induced hypotension, marked depression of the EEG or the CFM is seen, structural damage may be avoided if immediate measures are taken to increase MAP.

Changes in cortical ECF K^+*,* Ca^{2+} *and* H^+ *activities*

Below the MAP threshold for EEG depression lie the thresholds for K^+ release from and Ca^{2+} entry into cells, both these changes being indicative of severe cell membrane failure (Astrup et al., 1977; Harris et al., 1981; Heuser and Guggenberger, 1985). Histological ischaemic cell damage occurs close to the threshold for Ca^{2+} entry into the cells. It has been demonstrated that the MAP threshold for K^+ escape into the ECF in the cerebral cortex is higher during TMP-induced hypotension than in NTP-induced hypotension (figs 1, 2) (Morris et al., 1983). It would therefore seem that there are differences in the threshold MAP values for cell membrane failure in the cerebral cortex with different hypotensive drugs and that, in clinical circumstances which require the induction of severe hypotension, NTP may be the drug of choice.

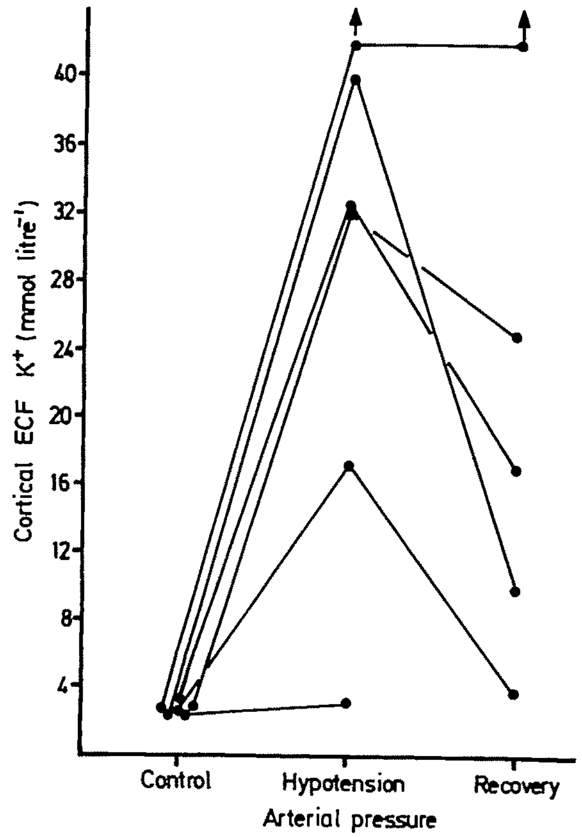

FIG 1. Brain cortical ECF potassium concentrations at control arterial pressure, during hypotension and in the recovery period, in cats subjected to trimetaphan hypotension with beta blockade. Arrows = > 40 mmol litre^{-1} (Reproduced after Morris and others (1983), by kind permission of the editor and publishers)

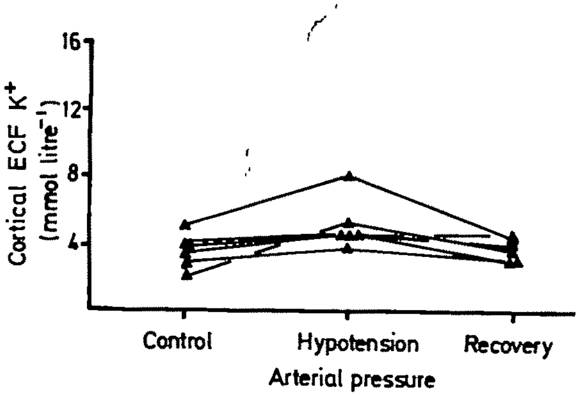

FIG 2. Brain cortical ECF potassium concentrations at control arterial pressure, during hypotension and in the recovery period, in cats subjected to nitroprusside hypotension with beta blockade. (Reproduced after Morris and others (1983), by kind permission of the editor and publishers.)

During induced hypotension, an extracellular fluid acidosis develops in the cortex, and presumably elsewhere in the brain. This acidosis results in part from carbon dioxide accumulation secondary to reduced CBF, but its severity indicates that there must be a major metabolic component. Measurement of tissue lactate concentrations confirms this. The decrease in pH, unlike the changes in ECF K$^+$ and Ca^{2+}, is not a threshold phenomenon. pH starts to decrease at values of MAP which are well above the threshold values and the development of acidosis is a function not only of MAP, but also of duration of hypotension. Blood loss occurring during hypotension rapidly increases the acidosis and, as discussed by Siesjö and Wieloch (1985) in this Symposium, the degree of acidosis is influenced by the plasma glucose concentration.

The severity of the acidosis is surprising. Values as low as pH 5.5 have been measured during TMP-induced hypotension in the cat (Morris et al., 1983) and, during induced hypotension, these values occur because the residual reduced flow continues to deliver glucose to a brain which metabolizes it anaerobically to lactate because of the low oxygen supply. The acidosis is less severe during NTP-induced hypotension. It is likely that severe extracellular acidosis is in part responsible for ischaemic cell damage, although this is not completely established. It is certainly true that complete recovery is commonly seen in animals following hypotension which has caused marked ECF acidosis.

It has been demonstrated that the severity of the tissue acidosis in conditions of partial global ischaemia is related partly to the plasma glucose concentration; the greater the plasma glucose concentration, the more glucose enters the brain, where it is metabolized anaerobically to lactate, with a worsening of the tissue acidosis (Siesjö and Wieloch, 1985). The usual preoperative starvation regimen practised clinically probably reduces the brain acidosis which occurs during intraoperative hypotension by maintaining low values of plasma glucose. For the same reason, glucose infusions during surgery should probably be avoided before induced hypotension.

Restoration of normotension

In animal studies, restoration of normotension (by stopping hypotensive drug infusion and re-infusion of withdrawn blood) results in normalization of K$^+$ and pH values, provided the time lag between K$^+$ release and the recovery of MAP is not too great. The time required for normalization of pH depends on the severity of the acidosis, but, in the cat, an acidosis in the range pH 5.5–6.0 takes more than 30 min to resolve. During this period there is rebound hyperaemia in the cerebral circulation when arterial pressure is fully restored and this hyperaemia probably results from tissue acidosis. However, the normalization of pH, K^+ and Ca^+ and the return of some electrical activity does not guarantee that areas of ischaemic cell damage have not resulted from the hypotensive exposure.

After the stage of hyperaemia there follows a period of hypoperfusion and it has been suggested that this low CBF during recovery from an ischaemic insult may contribute to the final extent of the ischaemic cell damage (Ginsberg, Budd and Welsh, 1978). Attempts have therefore been made to protect the brain from this secondary hypoperfusion by administering barbiturates (Nordstrom and Rehncrona, 1977; Steen, Milde and Michenfelder, 1978). The aetiology of this secondary period of hypoperfusion is not well understood, although it has been demonstrated that the administration of calcium entry blocking drugs improves blood flow, which perhaps indicates that movement of calcium from the extracellular space into the vascular smooth muscle cells is a factor (Steen et al., 1983).

Brain oedema

Klatzo (1985) has reviewed the subject of brain oedema in this Symposium and made the distinction between vasogenic and cytotoxic oedema. A question relevant to this review is: Does oedema occur after profound arterial hypotension?

Symon, Branston and Chikovani (1979) have shown that brain water increases if CBF decreases to less than 20 ml min^{-1}/100 g, that is at values of flow which may occur during the clinical use of hypotension and which lie close to those at which the EEG voltage decreases, but above the thresholds for K^+ and Ca^{2+} movements. This excess brain water is, presumably, moving to the intracellular space, as a result of increases in the number of osmotically active small molecules produced by partially anaerobic metabolism. This, then, would be a form of cytotoxic oedema and is usually reversible on restoration of MAP. If the degree of ischaemia is more severe, so that blood flow decreases to the threshold for failure of cell membrane ion haemostasis, that is flows less than 10 ml min^{-1}/100 g, then further cytotoxic oedema occurs as a result of movement of sodium into cells. This form of oedema, which probably rarely occurs during induced hypotension, is also reversible unless the cell has been so severely damaged as to proceed to ischaemic cell death (Hossman, 1976; Iannotti and Hoff, 1983).

The hyperaemia which occurs early in the recovery period results in an increase in brain bulk and increases intracranial pressure in the closed skull. This hyperaemia subsides rapidly after induced hypotension, certainly within 60 min and usually within 15 min. If MAP is allowed to increase rapidly to hypertensive values in this very early stage of recovery, fluid containing plasma proteins may be forced through the dilated capillary walls to produce vasogenic oedema (Klatzo, 1985). It is possible that the presence within the circulation of vasodilatory drugs, such as nitroprusside or halothane (Forster et al., 1978) may accentuate this vasogenic oedema. Ishikawa and colleagues (1983) have demonstrated, in dogs, the penetration through the blood–brain barrier of Evans Blue (a dye which attaches to plasma albumin) following induced hypotension with nitroprusside, but not after trimetaphan. It is probably good practice, therefore, to allow arterial pressure to recover rather slowly after induced hypotension, especially if a direct dilator such as nitroprusside has been used, in order to avoid vasogenic oedema. On the other hand, it is known that, following total circulatory arrest, re-perfusion may be patchy and that the uniformity of blood flow is improved by a rapid return of MAP. The situation is therefore unclear, but it is probably true that the degree of cerebral ischaemia which could occur during deliberately induced hypotension (in the absence of circulatory arrest) is not severe enough to cause patchy re-perfusion and so, in the author's opinion, restoration of MAP should be gradual over 10–20 min. It is important to remember that ischaemia itself rarely results in vasogenic oedema in the early recovery period because the blood brain–barrier is resistant to ischaemic damage. It is the combination of hypertension, cerebral vasodilatation and hyperaemia which causes postischaemic vasogenic oedema.

If the brain ischaemia during induced hypotension has been severe enough, neurones are damaged irreversibly, particularly in the selectively vulnerable areas — that is the boundary zones, hippocampus and basal ganglia. Brain oedema in these areas of dying cells continues to progress and may lead to compression of surrounding capillaries, with further ischaemia and extension of the area of infarction (Ames and Nesbitt, 1983). In these circumstances the blood–brain barrier may again become permeable to plasma proteins, resulting in increased oedema formation.

The management of a patient who is thought to have suffered brain ischaemia during induced hypotension requires treatment for brain oedema spreading from the foci of neuronal cell death: controlled hyperventilation and infusion of hypnotic drugs. Mannitol is probably also valuable, except at times when the blood–brain barrier is "open". Unfortunately, at present there is insufficient knowledge to define when this occurs in man.

In summary, a degree of cytotoxic oedema may occur after profound induced hypotension, and this is reversible within 1 h. Vasogenic oedema may occur if MAP is allowed to increase rapidly at the end of hypotension, especially in the presence of vasodilator drugs. Irreversible cytoxic oedema occurs only with ischaemic cell death, but may lead to an extension of the area of infarction by compressing local blood vessels as a result of increased local tissue swelling and pressure. In these circumstances, the blood–brain barrier may open to plasma proteins.

FOCAL ISCHAEMIA

Up to this point we have discussed only the normal cerebral circulation. Congenital variations in the Circle of Willis are not uncommon and, in some patients, these may cause shifts in the location of the boundary zones. The main effect of pathology of the cerebral circulation, however, is to render some area of the brain more susceptible to ischaemia from induced hypotension. A common example would be atheromatous narrowing of the internal carotid artery resulting in a low intravascular pressure on the ipsilateral side, with the possibility of ischaemic flow values, particularly in the middle cerebral artery territory. Whether ischaemic damage occurs or not in such a patient depends on the level of hypotension used and the adequacy of the collateral circulation through the Circle of Willis and on the cortical surface. The problem with such patients is that the anaesthetist has no knowledge of the vascular pathology, which may be clinically silent (fig. 3). It is the possibility of clinically silent partial obstructions to flow, together with variations in the efficacy of the collateral vascular supply, either at the Circle of Willis or at the pial surface, which makes it impossible to generalize on the lowest arterial pressure which may be tolerated by the brain and which indicates the importance of monitoring electrical activity (Prior, 1985).

The sequence of electrical and ionic events which occur in focal ischaemia is the same as that reviewed above for global ischaemia during induced hypotension and the relationship between local ischaemia and local intravascular pressure is identical. However, the local intravascular pressure distal to the site of partial vascular obstruction is much lower than the systemic arterial pressure, which would be the pressure monitored by the anaesthetist.

The main differences between global and focal ischaemia are:

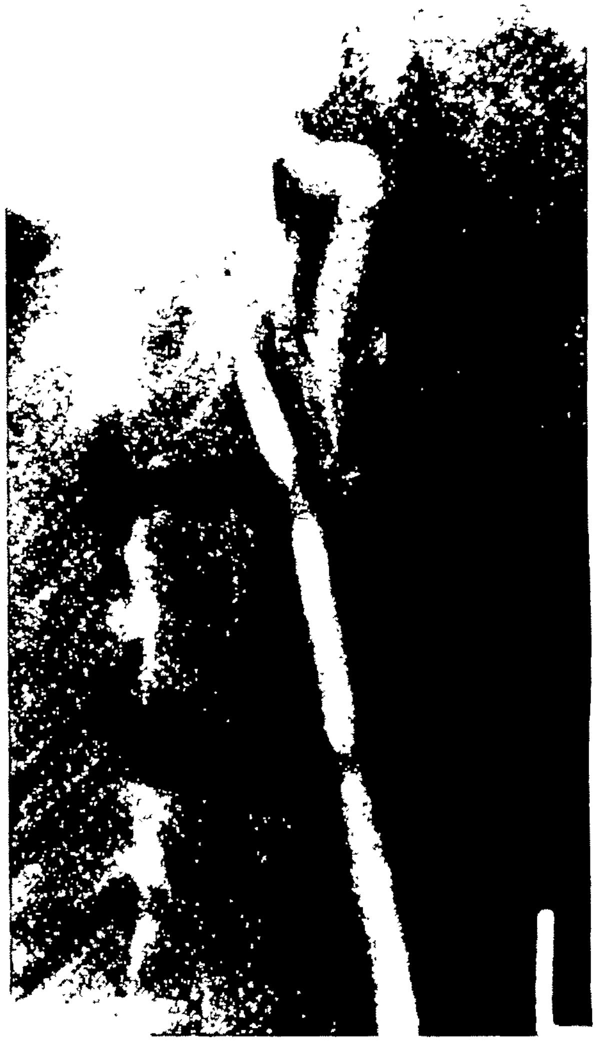

FIG. 3. Carotid angiogram showing fibromuscular dysplasia of the internal carotid artery. The condition consists of segmental overgrowth of the fibrous and muscular tissues of the media of the artery and is usually symptomless, although associated with an increased incidence of intracranial aneurysms. The induction of hypotension in a patient with this condition could have marked effects on cerebral perfusion.

(i). In focal ischaemia, there is a central densely ischaemic zone surrounded by a rim of partial ischaemia (this is often termed the "penumbra" (Astrup et al., 1977)—a word which originally described the rim of partial shadow during an eclipse of the sun).
(ii). The presence in focal ischaemia of maintained perfusion in the surrounding territories of arterial supply.

It is because of these two factors that vasoactive anaesthetics can influence the perfusion of the ischaemic cells, especially the cells in the penumbra zone, by constricting or dilating surrounding vascular territories, so inducing "steal" or "inverse steal" through collateral circulations, mainly at the pial surface.

ANAESTHETIC TECHNIQUES

General considerations

Some hypotensive drugs maintain cerebral perfusion better than others, presumably because they cause more marked cerebral vasodilatation. However, dilatation of the circulation may not be beneficial if it causes steal of blood away from a partially ischaemic area (in focal ischaemia); for example, the administration of NTP to a patient with unilateral internal carotid stenosis might increase flow on the contralateral hemisphere at the expense of the at-risk hemisphere. Smith and colleagues (1974) demonstrated that halothane increased the area of infarction following experimental middle cerebral artery occlusion, presumably by this mechanism. In circumstances of focal ischaemia, vasoconstrictive drugs may therefore be preferable, for example a thiopentone infusion.

An additional disadvantage of vasodilators is the increase in ICP produced, and this results in a decrease in cerebral perfusion pressure during hypotension. This factor, however, is only operative until the dura has been opened, for thereafter ICP is close to atmospheric pressure.

Although vasoconstrictor drugs decrease ICP and might therefore be advocated for this reason, the change produced is small in a patient whose ICP is normal. The situation is different, however, if ICP is increased as a result of intracranial tumour or oedema following recent subarachnoid haemorrhage. Cerebrovascular spasm is a problem when induced hypotension is used following subarachnoid haemorrhage, since reduced arterial pressure may exacerbate ischaemia in the territory of the spasm.

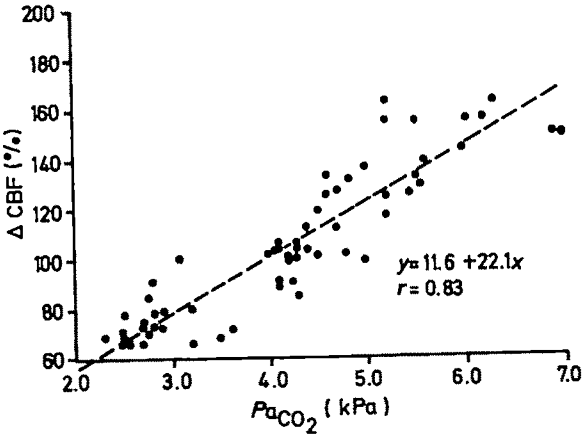

FIG 4. Changes in cortical blood flow in the cat during alterations in arterial PCO_2 over the range 3–7 kPa during normotension. The usual linear relationship between flow and arterial PCO_2 in this range is demonstrated. (Reproduced from Gregory, Ishikawa and McDowall (1981), by kind permission of the editor and publishers.)

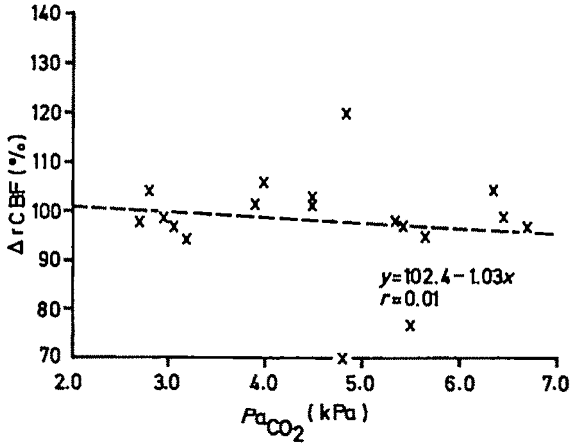

FIG 5 The relationship between cortical blood flow and arterial PCO_2 in the cat during trimetaphan-induced hypotension. No flow response to arterial PCO_2 change remains at a mean arterial pressure of 36–37 mm Hg. (Reproduced from Gregory, Ishikawa and McDowall (1981), by kind permission of the editor and publishers.)

Unfortunately, little is known of the effect of drugs on spasm, except in animal models, the relevance of which to clinical "spasm" is debated. The use of vasodilator drugs, however, may produce local areas of steal when spasm is present.

There is much debate on the optimal arterial PCO_2 during induced hypotension. Some authorities advocate spontaneous ventilation in order to produce normocapnia or mild hypercapnia, with a view to maintaining cerebral perfusion. However, Harper and Glass (1965) showed that changes in arterial $P\text{CO}_2$ during haemorrhagic hypotension did not influence cerebral blood flow and this has been demonstrated also to apply during hypotension induced with halothane (Okuda et al., 1976) or trimetaphan (Gregory, Ishikawa and McDowall, 1981) (figs 4, 5). With nitroprusside, cerebral blood flow is greater during hypotension and therefore the cerebral vessels show some continuing but reduced sensitivity to $P\text{CO}_2$ change (Gregory, Ishikawa and McDowall, 1981). It seems that, when flow decreases to the level at which EEG depression occurs, there is no responsiveness to $P\text{CO}_2$ change. At greater arterial pressures there is some reduced carbon dioxide responsiveness.

In the presence of focal pathology (atheroma or spasm) increases in carbon dioxide may be detrimental, as a result of the "steal" mechanism. However, since spasm affects medium-sized vessels and carbon dioxide changes affect small arteries and arterioles, a low carbon dioxide concentration, combined with spasm, may produce two segments of increased vascular resistance in series and reduce flow to very low values. This disadvantage may outweigh the possibility of achieving inverse steal by hypocapnia. Most clinicians conclude from these experimental findings that induced hypotension is probably best conducted at arterial $P\text{CO}_2$ values of approximately 4 kPa.

Choice of hypotensive drugs

Beta blockers seem to have little direct action on the cerebral circulation. TMP acts mainly by ganglion blockade, with little dilator action on the cerebral vessels, as indicated by the lack of increase in ICP with this agent (Turner et al., 1977). As already discussed, the autoregulation curve shows better-maintained perfusion, compared with haemorrhagic hypotension. Other ganglion blockers such as pentolinium and hexamethonium probably resemble TMP in their cerebrovascular effects. NTP produces better cerebral perfusion at low MAP than does TMP, presumably because of its potent direct dilatory action, and nitroglycerine behaves similarly. Where very low arterial pressures are required for short periods, NTP is probably the agent of choice, provided its toxic limit is kept in mind. However, it does markedly increase ICP (Turner et al., 1977), an effect which is even greater with nitroglycerine (NG) (Rogers and Traystman, 1979). Also, the marked dilatation may produce steal in circumstances of focal ischaemia when TMP would have the advantage. Grubb and Raichle (1982) reported that cerebral oxygen utilization was increased during NTP hypotension in baboons under ketamine–nitrous oxide–oxygen anaesthesia. This would be disadvantageous, but concomitant anaesthesia with halothane or other volatile agents would probably block such an increase in oxygen requirements.

Adenosine triphosphate (ATP) has been used in a few centres for some years for inducing hypotension and at present there is increasing interest in this agent. It is a dilator of the cerebral circulation and may probably be considered to be in the same group as NTP and NG in its effects on CBF, ICP and autoregulation (Van Aken et al., 1984). It would therefore be anticipated that ATP, in common with NTP, may allow MAP to be reduced markedly without producing cell membrane failure, but a preliminary report from Heuser, Morris and Guggenberger (1984) suggests that this may not be the case. As yet, there is inadequate evidence on the profile of ATP action.

Choice of anaesthetic drugs

Both thiopentone and Althesin reduce cerebral metabolism and CBF. Their cerebral vasoconstrictive action might be advantageous in focal ischaemia through the inverse steal mechanism (Rasmussen, Rosendal and Overgaard, 1975). Their action in reducing ICP tends to provide a higher perfusion pressure for a given systemic hypotension, provided the dura is closed. The inverse steal and the ICP effects probably account for the observation, in experimental animals, that the size of an infarct following temporary focal ischaemia is smaller when these drugs have been given (Smith et al., 1974). If hypnotic drugs of this group are given in high dosage with the objective of protecting the brain, EEG and CFM monitoring to detect ischaemia become insensitive and unreliable (Prior, 1985).

Nitrous oxide, halothane, enflurane and isoflurane are cerebral vasodilators. Despite this disadvantage volatile anaesthetics are commonly used to potentiate the i.v. hypotensive drugs. Inspired concentrations of halothane up to 1% and enflurane up to 1.5% are used for this purpose but, should circulatory arrest occur, cardiac resuscitation may be difficult (Prys-Roberts et al., 1974). Isoflurane is likely to become the agent of choice for supplementing the hypotensive effect of drugs such as TMP, since it reduces MAP and cerebral metabolic activity with only moderate cerebral vasodilatation (Newberg, Milde and Michenfelder, 1983). Indeed, Lam and Gelb (1983) were able to produce satisfactory hypotension with isoflurane alone.

General anaesthetic considerations

The margins of safety in respect of cerebral ischaemia are narrowed by the use of induced hypotension, so that any anaesthetic accident or mistake which would be only temporarily embarrassing under normal circumstances, may have catastrophic effects during induced hypotension. Anaesthetic technique must be meticulous: the airway must be absolutely secure, for an incident of hypoxia in a situation of marginally adequate cerebral perfusion could result in ischaemic brain damage, and could also cause sudden cardiac arrest. It should be remembered that a short period of total cardiac arrest following a period of low cerebral perfusion during induced hypotension would be more damaging to the brain because of the pre-existing cerebral tissue acidosis. Induced hypotension impairs pulmonary gas exchange and an increase in inspired oxygen to 40 or 50% is required to maintain full saturation of haemoglobin in many patients. Equally dangerous during induced hypotension is an incident of partial or complete obstruction on the expiratory side of the anaesthetic circuit, which produces a further dramatic decrease in MAP and an increase in central venous pressure.

Cerebral ischaemia may occur, not only in the operating theatre, but also in the recovery room, or after the patient has returned to the ward. For example, partial airway obstruction may occur in a patient still moderately hypotensive in the early period after operation, leading to cardiac arrest. Alternatively, severe orthostatic hypotension may result from propping the patient up in bed on return to the ward, as a result of persisting sympathetic blockade produced either by ganglion-blocking drugs or extradural or spinal anaesthesia.

Of course, the final arbiter of the avoidance of brain ischaemia from induced hypotension is the postoperative condition of the patient. However, it is very difficult to obtain firm evidence from mortality and morbidity surveys on the incidence of brain damage following induced hypotension, partly because of the possibly detrimental effect of anaesthesia, surgery and the primary pathology present. Older patients are commonly found to be less capable mentally after surgery and anaesthesia, whether or not induced hypotension has been used, whilst in young people the brain adapts so efficiently that even quite major degrees of ischaemic damage can be missed clinically.

The literature on mortality and morbidity surveys up to 1975 has been well-reviewed and critically assessed by Lindop (1975). He pointed out that the interpretation of data on mortality and morbidity from large series is impeded by lack of comparable control groups not subjected to induced hypotension. On the other hand, in the smaller series in which more subtle and time-consuming tests of cognitive and neurological function have been performed (including control groups) the small sample size precludes assessment of the incidence of complications. Nonetheless, he noted that all large reported series contain one or two anaesthetic deaths attributed to induced hypotension and he considers that a survey of the literature indicates a mortality incidence of 1 in 167 and a morbidity incidence of 1 in 39. The complications were mainly cerebral thrombosis, presenting as failure to recover consciousness or neurological deficits. Other complications included myocardial infarction and retinal artery thrombosis. Perhaps it needs to be emphasized again that these figures cannot be interpreted to indicate the degree of risk associated with induced hypotension in the absence of control data. Furthermore, the papers on which Lindop (1975) based these calculations extended back to the 1950s, when knowledge of the techniques and the availability of monitoring were much less than today. It is to be hoped, although it has not been proved, that hypotension is now safer than it was 20 years ago.

CONCLUSIONS

(1) Cerebral perfusion is better maintained during drug-induced hypotension; of the drugs commonly used, perfusion is maintained best with nitroprusside.

(2) As a result of (1), cortical PO_2 and electrical activity are least disturbed during hypotension when nitroprusside is used. The arterial pressure at which ischaemic failure of cell membrane function occurs is lower with nitroprusside than with trimetaphan.

(3) At low values of arterial pressure, hypocapnia does not further reduce CBF.

(4) Cerebral metabolic depressant drugs such as thiopentone and isoflurane may have a place in clinical techniques of induced hypotension.

(5) A short period of hyperperfusion and loss of autoregulation follows induced hypotension and indicates a need to avoid hypertension in the recov-

ery stage. There may be a later stage of hypoperfusion.

(6) Cytotoxic oedema may occur in the first hour following recovery from extreme hypotension. The blood–brain barrier may open also at the end of hypotension, especially if the arterial pressure is allowed to increase above control values in the presence of dilator drugs such as nitroprusside.

(7) Margins of safety are narrowed during the use of induced hypotension and therefore the technique should be used only when it may benefit the patient and only by those trained and experienced in the method.

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subsequent brain damage. After complete circulatory arrest when the vascular bed has been flushed by clear solutions, restitution of circulation to the brain usually results in a uniform and hyperaemic reperfusion. In the experimental studies of Lewelt, Jenkins and Miller (1980) reperfusion of the brain was attempted after arterial pressure had been decreased to less than 30 mm Hg. In control, uninjured, animals, restoration of the arterial pressure resulted in resumption of normal or greater than normal values of cerebral blood flow and subsequent alterations in arterial pressure produced a pressure-passive change in blood flow, signifying failure of autoregulation. However, in none of the animals that had been subjected to concussive head injury was adequate cerebral blood flow restored, even at normal values of arterial pressure. The combination of concussive trauma and arterial hypotension appeared to interfere with subsequent reperfusion of the brain. This situation may have parallels in human head injury where the intracranial pressure has increased so close to the level of arterial pressure that effective cerebral circulation has ceased. In the small number of such patients studied, arteriography or measurements of cerebral blood flow performed after intracranial pressure has been reduced by drainage of ventricular CSF and cerebral perfusion pressure has been restored, have failed to demonstrate a resumption of cerebral blood flow (Miller and Adams, 1972).

Arterial hypoxaemia

In the minutes and hours that follow a severe head injury, there are multiple causes of hypoxaemia, including prolongation of the apnoea that follows the injury, atelectasis, aspiration of vomited material and concomitant injuries to the lung and chest wall. In addition, brain damage may produce highly abnormal breathing patterns (North and Jennett, 1974). When arterial hypoxaemia becomes sufficiently severe to cause desaturation of haemoglobin, cerebral vasodilatation occurs (McDowall, 1966). This process may result in tripling of cerebral blood flow, with an increase in cerebral blood volume and a consequent increase in intracranial pressure. In injured brain, however, there may be attenuation of the vasodilator response to hypoxaemia, and to changes in arterial $P\text{CO}_2$. This has been observed in patients (with head injury) in whom multiregional blood flow measurements have been made and in experimental animals subjected to controlled-intensity concussional injuries (Enevoldsen and Jensen, 1978; Lewelt, Jenkins and Miller, 1982). Loss of responsiveness to changes in blood-gases occurs at a greater degree of injury and insult than loss of autoregulation and complete absence of the response to change in $P\text{O}_2$ and $P\text{CO}_2$ is usually seen only as a pre-terminal event (Obrist et al., 1979; Overgaard and Tweed, 1979). However, impairment of the response may explain why the patient with severe head injury tends to suffer a more severe and lasting neurological deficit after an episode of hypoxaemia than does a normal patient. Early arterial hypoxaemia in head injured patients is clearly associated with an increase in morbidity and mortality (Price and Murray, 1972; Miller et al., 1981).

TABLE III. *Increased intracranial pressure in severe head injury. incidence and influence on outcome*

Intracranial pressure	No. of patients	Mortality
Not significantly increased (0–20 mm Hg)	95 (47%)	19%
Moderately increased (21–40 mm Hg)	67 (33%)	28%
Severely increased (41–80 mm Hg)	39 (20%)	79%
Total	201 (100%)	34%

Increased intracranial pressure

Intracranial hypertension is common after head injury and is associated with increased mortality. (table III). The most common causes for increased intracranial pressure soon after head injury are intracranial haematoma, congestive brain swelling and traumatic subarachnoid haemorrhage. Miller and his colleagues (1977) noted increased intracranial pressure in all but two of 62 patients with post-traumatic intracranial haematoma before surgical decompression and in more than half of all severely head injured patients even after decompression had been carried out (Miller et al., 1981). Since intracerebral venous pressure is maintained at a value just above the mean intracranial pressure, cerebral perfusion pressure (the difference between intracerebral arterial and venous pressures) is well approximated by the difference between systemic arterial pressure and intracranial pressure (Miller, Stanek and Langfitt, 1972; Johnston and Rowan, 1974). In the absence of a compensatory increase in arterial pressure, an increase in intracranial pressure therefore implies a reduction in cerebral perfusion pressure, in addition to one in transmural pressure.

When perfusion pressure is reduced by progressively increasing ICP, cerebral blood flow can be maintained relatively constant by the same process of autoregulation until perfusion pressure decreases to 40 mm Hg. If perfusion pressure decreases below this value there is a dramatic reduction in cerebral blood flow. If autoregulation is impaired, cerebral blood flow varies passively with perfusion pressure, whether this is changed by primary alterations of arterial or of intracranial pressure.

The degree to which CBF changes with variation in perfusion pressure is a function of the residual cerebrovascular resistance. In a hyperaemic circulation with a low level of resistance, there is pronounced alteration in blood flow with relatively small changes in perfusion pressure (Miller, Stanek and Langfitt, 1973). However, when resting resistance is high, as in intravascular stasis or perivascular oedema, resting cerebral blood flow is already reduced and the passive changes in flow induced by changes in perfusion pressure are relatively small. Miller and Reilly and their colleagues studied the effects of changes in arterial pressure on cerebral blood flow in animals that had been subjected to cryogenic brain injury and increased intracranial pressure. In areas of brain oedema adjacent to the lesion, there was attentuation of the cerebral vasodilator response to carbon dioxide, but increased arterial pressure did not result in significant increase in regional CBF (Miller et al., 1976; Reilly, Farrar and Miller, 1977). In another series of experiments, Leech and Miller (1974) showed that, when intracranial pressure is already increased, progressive increase of arterial pressure causes an increase in brain elastance. This increase in the "stiffness" of the brain implies that any subsequent addition of volume to the craniospinal axis (blood, CSF or mass lesion volume) results in a great increase in ICP (Langfitt, 1969; Miller, 1975; Sullivan, Miller and Searles, 1980).

Because of this, the deliberate induction of increases in cerebral perfusion pressure in head injured subjects by increasing arterial pressure and attempting to control ICP may be both ineffective in restoring cerebral blood flow, because of the increasing level of vascular resistance that is encountered, and dangerous because of an increased liability to intracranial hypertension. The apparent fixity of a reduced cerebral blood flow despite increasing perfusion pressure, is one form of false autoregulation. The second type of false autoregulation encountered in the severely damaged brain occurs when an increase in arterial pressure is accompanied by an equal increase in ICP so that there is no net change in perfusion pressure and thus no stimulus to autoregulation (Fieschi et al., 1974). In both of these circumstances, however, any reduction in arterial pressure causes a further reduction in cerebral blood flow.

Brain shift, distortion and herniation

Since computerized tomography became the principal investigative method in severely head injured patients, the major revelation has been the high proportion of intracranial haematomas encountered in severely head injured (comatose) patients—40–50% in most series. Intracranial haematomas, particularly the intradural haematomas (subdural and intracerebral) are associated with a high incidence of increased ICP and high mortality (table IV) (Becker et al., 1977; Jennett et al., 1979; Miller et al., 1979).

During enlargement of mass lesions in the supratentorial compartment, medial temporal structures herniate through the tentorial hiatus. This process serves not only to interrupt the free communication of CSF pressure throughout the craniospinal axis, but the advancing temporal lobe can also compress the posterior cerebral artery to produce infarction of the ipsilateral occipital lobe. Subfalcine herniation of the cingulate gyrus may compress one or

TABLE IV. *Intracranial haematoma complicating severe head injury: incidence and influence on outcome*

	U.S. series			U.K. series		
Location of haematoma	No.	(%)	Mortality (%)	No	(%)	Mortality (%)
Extradural	18	8	28	10	11	20
Intradural	75	35	64	38	41	53
No discrete haematoma	132	59	18	45	48	44
Total	225	100	34	93	100	45

emphasized. When arterial pressure increases steeply in the head-injured patient, it is nearly always secondary to brain shift or an increase in intracranial pressure, or both. The correct way to treat this is to reduce intracranial pressure. To reduce arterial pressure alone results in rapid onset of severe brain ischaemia which is usually irreversible and leads to brain death.

Patients with severe head injuries may develop ECG multiple changes and cardiac arrhythmias suggestive of myocardial ischaemia. In fatal cases, subendocardial haemorrhage and focal myocytolysis are seen in the myocardium (Connor, 1968). The value of attempting to treat these cardiac changes, by β-adrenergic blockade for example, is not yet proven, but there are suggestions that this is beneficial.

worsening the patient's condition (table V). These measures include: more pronounced hyperventilation to a $P\text{aCO}_2$ of 2.5 kPa, continuous CSF drainage (from intraventricular catheters only) against a positive pressure of 3 kPa, and i.v. infusions of 20% mannitol solution.

Hyperventilation, by inducing hypocapnia, produces cerebral vasoconstriction, and reduces cerebral blood volume, and intracranial pressure. The degree to which ICP decreases depends on the extent of vasoconstriction and the elastance of the brain ($\Delta P/\Delta V$). Fears are often expressed that the decrease in cerebral blood flow produced by hypocapnia may cause ischaemic brain hypoxia. While it is true that hyperventilation can produce EEG slowing and CSF lactacidosis, structural brain damage has not been demonstrated. The curve relating CBF and arterial $P\text{CO}_2$ "bottoms out" as $P\text{aCO}_2$ decreases to less than 3 kPa.

TABLE V. *Methods of controlling increased intracranial pressure*

Treatment	Limitations	Risks
Hyperventilation	Blood vessels must be responsive to changes in $P\text{CO}_2$	Vasoconstriction may produce brain ischaemia (although structural damage has never been shown to occur)
CSF drainage	From ventricular catheter only	Leakage of CSF may interfere with ICP recording. Haemorrhage in track of cannula through brain
Mannitol	Serum osmolality must be less than 320 mosmol litre^{-1}	Fluid and electrolyte disturbance and renal failure
Barbiturates	Loss of neurological responsiveness	Arterial hypotension (especially in hypovolaemic patients); increased risk of infection
Gammahydroxybutyrate	Irritant solution, needs central venous line	Production of seizure-like EEG activity

Treatment of increased intracranial pressure

In the management of increased intracranial pressure, the objective is prevention of an increase in ICP sufficient either to cause a critical reduction in perfusion pressure and brain ischaemia or to produce worsening of brain shift or herniation, or both. The normal range of intracranial pressure is 0–15 mm Hg. When the pressure exceeds 22 mm Hg, measures should be initiated for the prevention of further increases in pressure. These measures must first include checking and correction of sources of increased intracranial pressure related to the position of the patient's head and neck, adequacy of the airway, body temperature and respiratory movements in opposition to the ventilator (Miller, 1978).

The next stage in management is the application of one or more of three measures which are known to be effective in most instances and carry a low risk of

Drainage of ventricular CSF may be a valuable means of controlling intracranial hypertension, but it is important to drain fluid only against a positive pressure in order to avoid collapse of the ventricular system, and loss of ICP recording. Because the normal practice is to insert the catheter to the contralateral ventricle when there is a unilateral intracranial haematoma or contusion, it is important to appreciate that, while CSF drainage may control ICP, it does not diminish midline brain shift and may even make it worse. This results because unilateral mass lesions causing increased ICP are frequently associated with enlargement of the contralateral ventricle. More often, however, in severe head injury of the diffuse axonal injury type, the ventricles are small, a ventricular catheter cannot be used and another means must be sought for reducing increased ICP. This is accomplished usually by i.v. infusion of hypertonic mannitol solution.

The mechanism of action of i.v. hypertonic agents in reducing ICP has been disputed for many years and the debate continues today. Initially it was considered that, by increasing the osmotic gradient between blood and brain, water would be drawn from oedematous brain, mass effect reduced and ICP would decrease (Wise and Chater, 1962). Because the blood–brain barrier is deficient in the centre of (but not throughout) oedematous brain, at that site mannitol leaks into the tissue and the maximal tissue-dehydrating effect is restricted therefore to normal rather than oedematous brain (Pappius and Dayes, 1965). More recently, Takagi and his colleagues (1983) demonstrated that i.v. hypertonic mannitol reduces the volume of CSF in the ventricles and postulated that ICP is reduced by this mechanism rather than a change in tissue water content. This supports the earlier observation of Reed and Woodbury (1962), who found no relationship between brain water content and ICP before or after administration of hypertonic urea.

Most recently, Muizelaar and his colleagues (1983) have proposed that the ICP reduction caused by mannitol is caused by cerebral vasoconstriction. This occurs as a response to an initial increase in cerebral blood flow produced by reduction in blood viscosity and appears to be an autoregulatory phenomenon, present only when autoregulation of cerebral blood flow has been preserved to changes in arterial pressure.

While the arguments for and against these operative mechanisms continue, the message for the managing clinician is clear. The administration of mannitol should be accompanied by continuous measurement of ICP. Hypertonic mannitol solution should be given in a dose of 0.5 g/kg body weight initially and later doses adjusted according to the intracranial pressure response first obtained. If the serum osmolality exceeds 320 mosmol litre^{-1} before infusion, mannitol should be withheld, as further administration is likely to produce impairment of renal function without benefit to the increased ICP.

For many years, corticosteroids have been advocated by many in the management of severe head injury (Faupel et al., 1976; Gobiet et al., 1976; Tornheim and McLaurin, 1978). Recent evidence has shown that steroid therapy neither reduces increased intracranial pressure in this situation nor improves outcome. Steroids therefore have no role in the overall management of patients with severe head injury, except perhaps in those patients in whom there is perifocal oedema around brain contusion. Even in these cases, steroids have not been conclusively beneficial; evidence from clinical trials is limited to severe head injury in general (Cooper et al., 1979; Gudeman, Miller and Becker, 1979; Pitts and Kaktis, 1980; Saul, Ducker and Salcman, 1981; Braakman et al., 1983).

If the first-stage measures to control increased ICP prove ineffective, it is important to exclude alterations in blood-gas tensions as a cause of increased ICP, or the development of a recurrent or delayed-onset intracranial space-occupying lesion, by CT. If these are not responsible, the treating physician is left with little alternative but to proceed with second-stage therapies. These have mainly comprised short-acting anaesthetic agents (barbiturates, Althesin, etomidate, gamma-hydroxybutyrate) (Turner et al., 1973; Shapiro, Wyte and Loeser, 1974; Escuret et al., 1979; Moss et al., 1979; Strong, 1984). Despite the claims that have been made for their efficacy in the short term control of increased ICP, there has not yet been conclusive evidence that the administration of any of these agents results in long term benefits to patients in the form of an increased survival rate or decreased morbidity (Miller and Teasdale, 1985).

Marshall, Smith and Shapiro (1979) pioneered the use of pentobarbitone in patients with severe head injury, in whom first line methods of therapy for increased ICP had failed. They reported a gratifying level of control of intracranial hypertension and an apparent reduction in mortality in their series of 100 patients as compared with other published series. This encouraging report led many to use the induction of barbiturate coma as a routine therapeutic measure in the management of severely head-injured patients (Rockoff, Marshall and Shapiro, 1979; Rea and Rockwold, 1983). In 1979, Miller reviewed the evidence in favour of barbiturate therapy for increased ICP, concluded that the case was not proven and called for experienced centres to conduct randomized trials (Miller, 1979b).

In a randomized trial recently completed at the Medical College of Virginia, the administration of pentobarbitone to severely head-injured patients resulted in some temporary control of increased intracranial pressure but failed to confer any overall benefit in terms of reduction of the incidence of increased ICP, death from increased ICP, reduction in the requirement for i.v. mannitol infusions or in mortality. However, in both control and barbitu-

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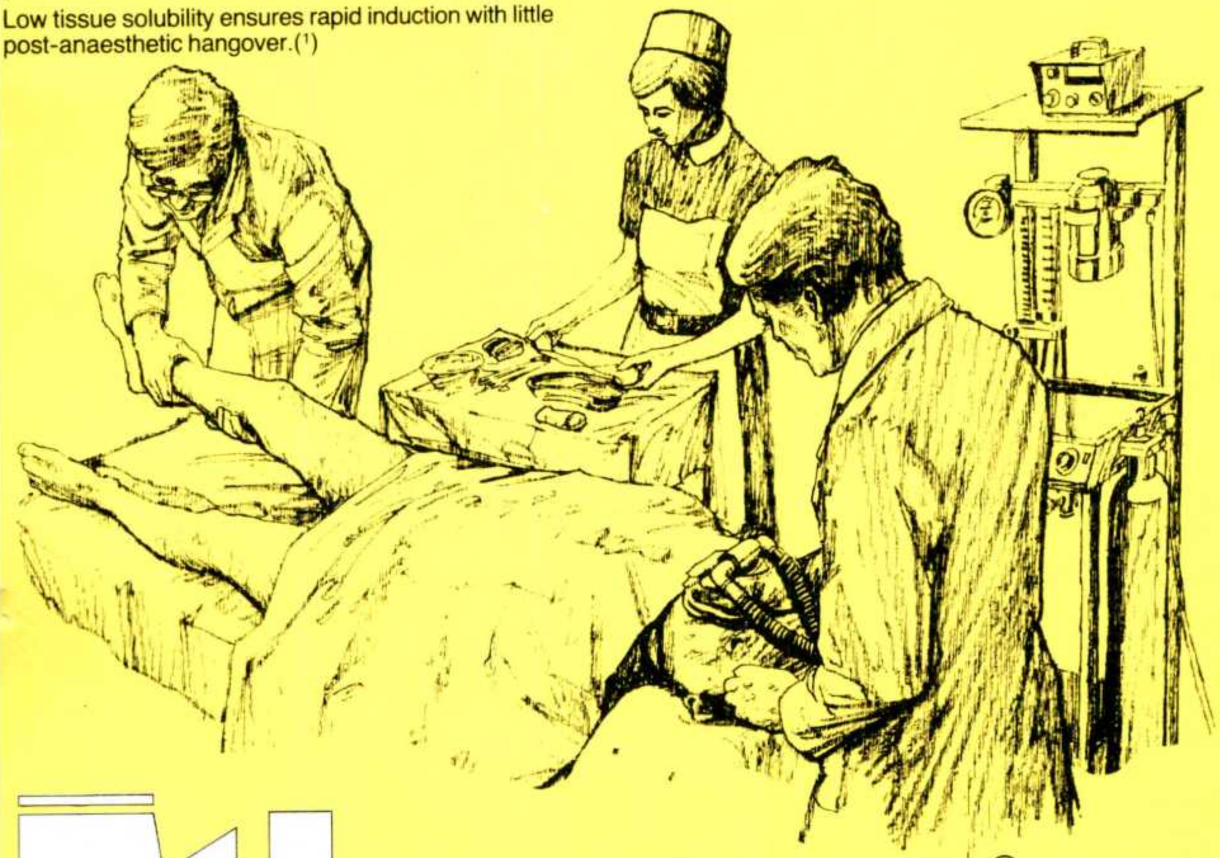

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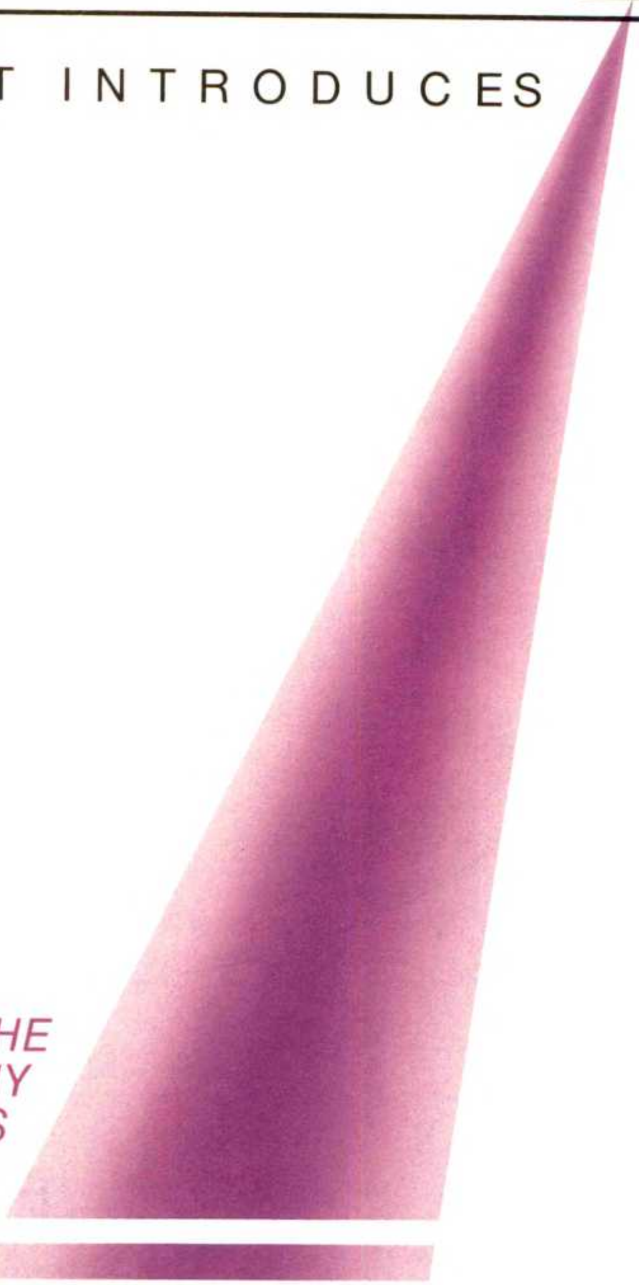

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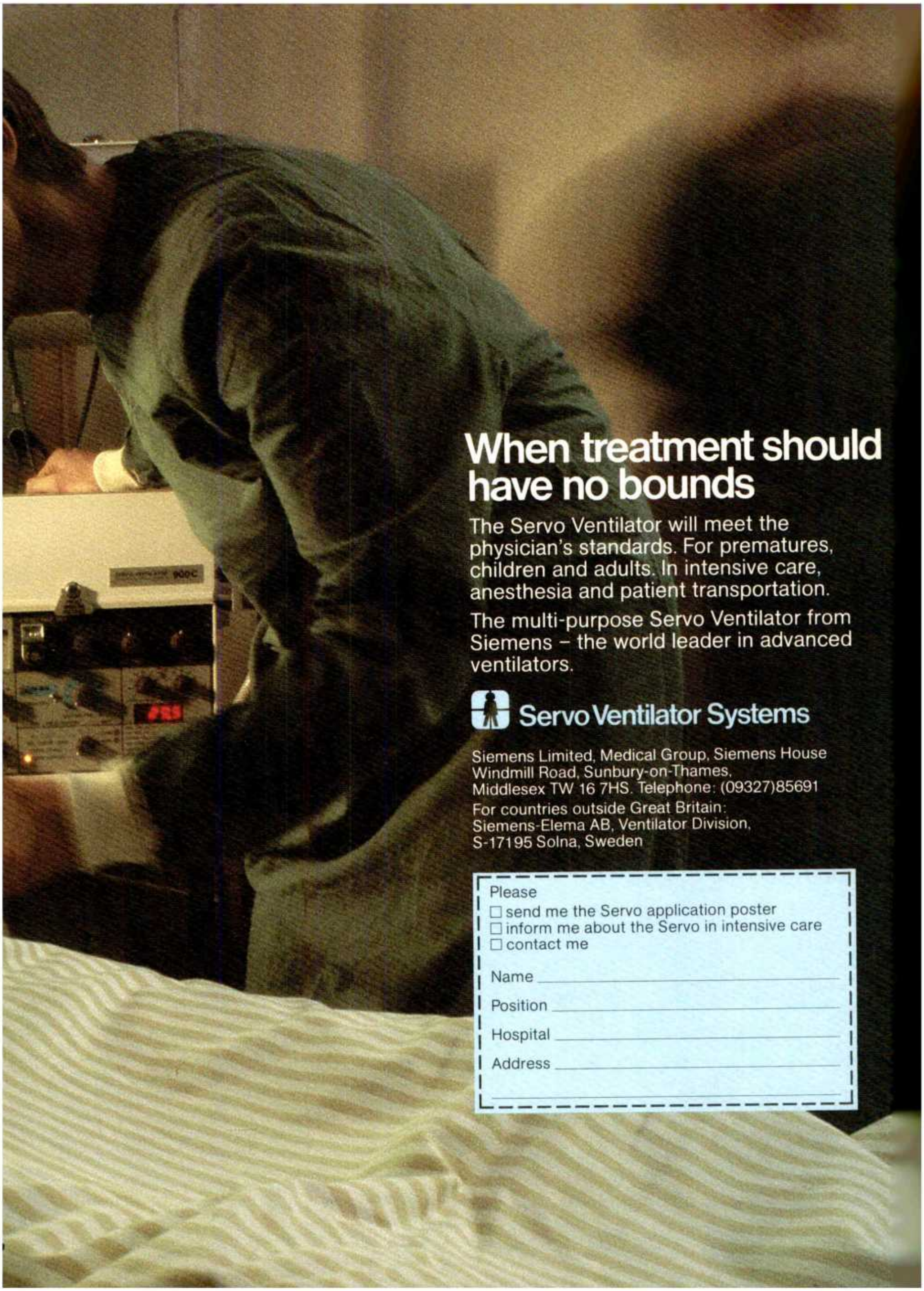

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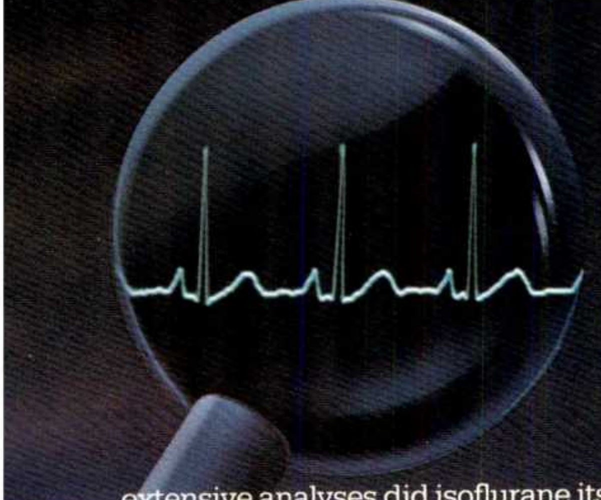

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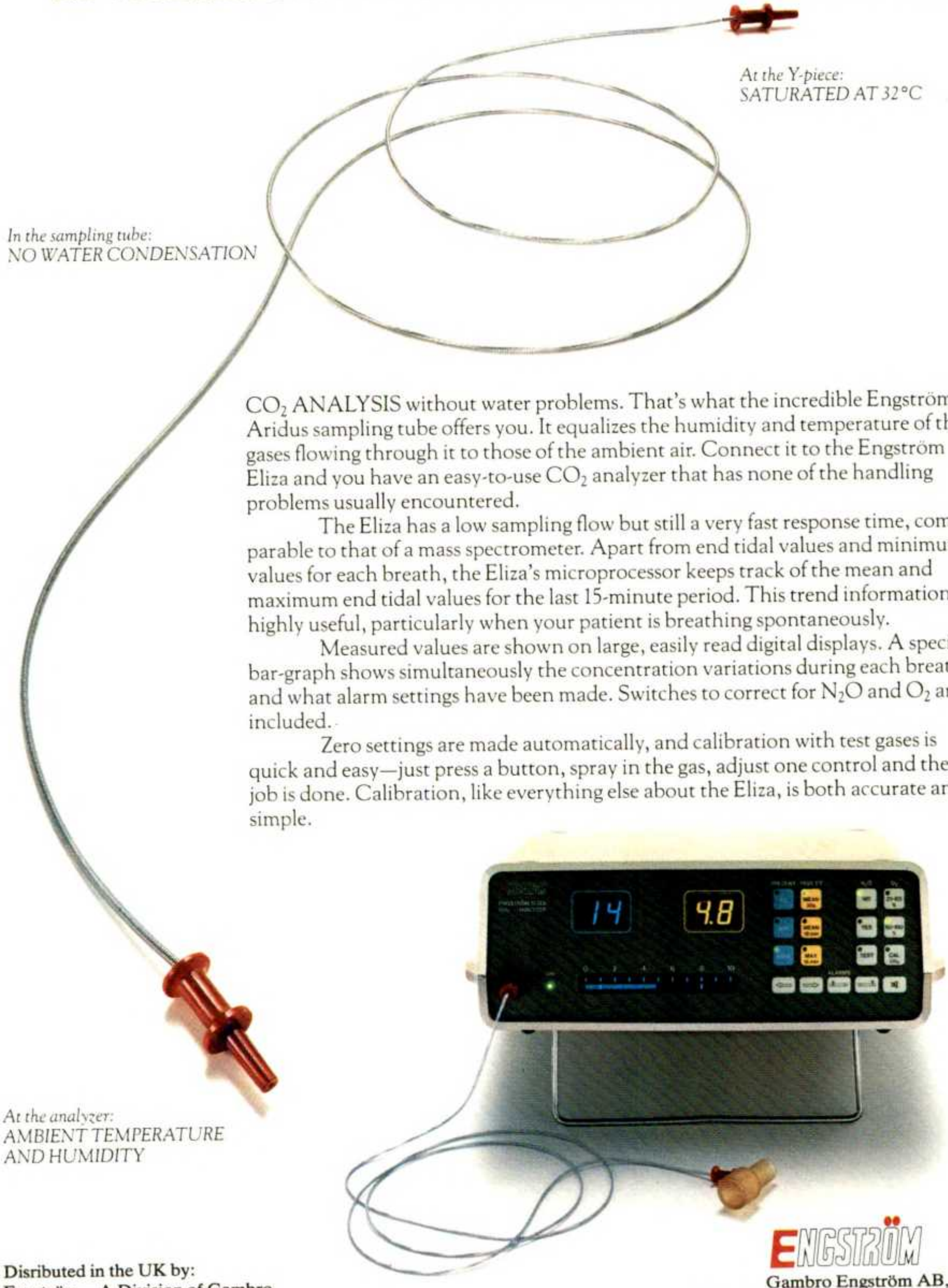

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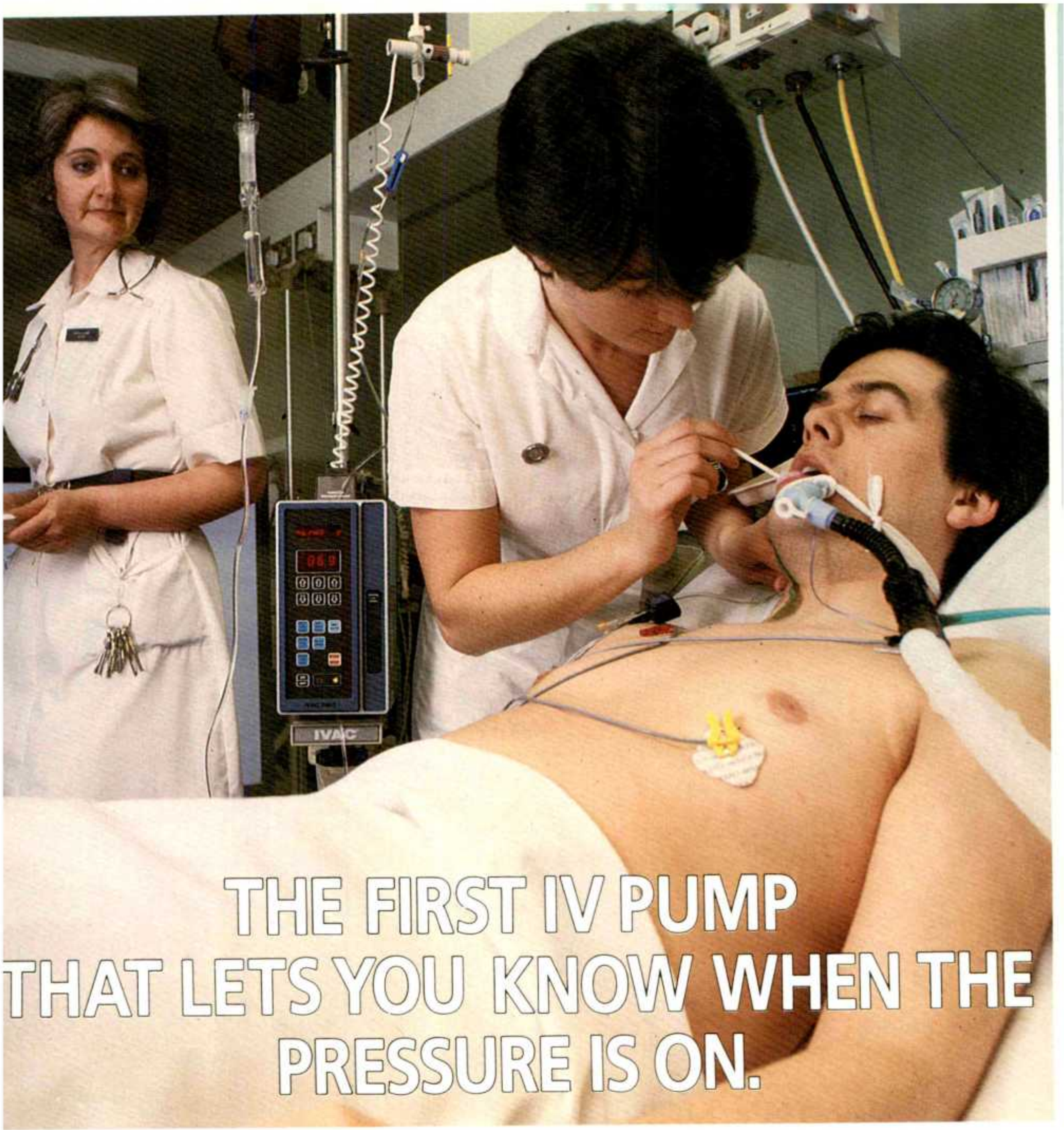

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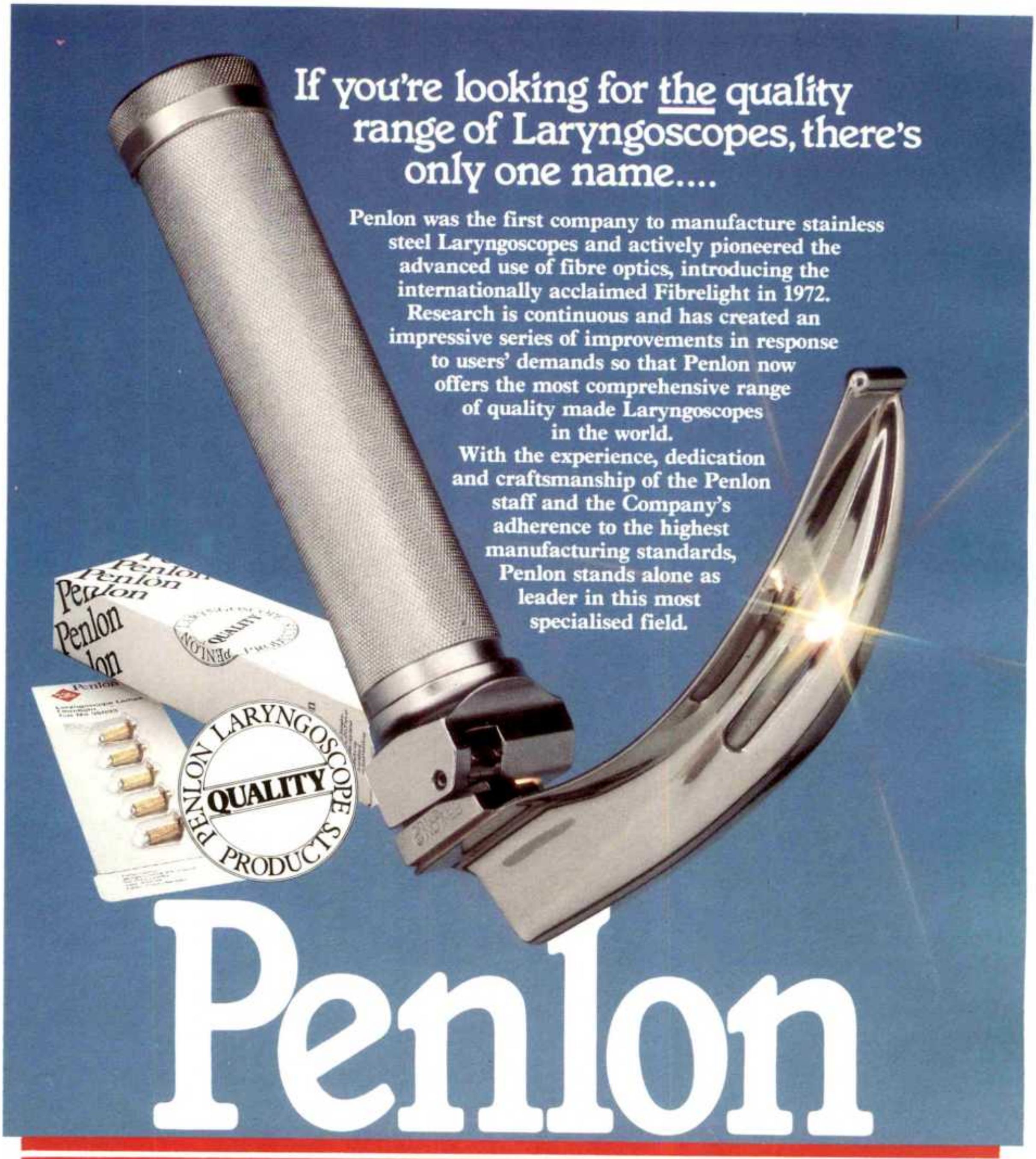

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EDITORIAL

RECEPTOR BINDING AND ITS SIGNIFICANCE

De Castro and Mundeleer (1959) devised the technique known as neuroleptanalgesia. Using fentanyl and droperidol in large doses, and providing controlled pulmonary ventilation with oxygen alone, they observed a neuro-vegetative state which had some characteristics in common with that which we call anaesthesia, and during which surgery could be performed. It is not surprising that they experienced difficulties in managing the recovery period, since many patients suffered persisting respiratory depression.

Following the discovery that the benzmorphan derivative pentazocine was not only an analgesic, but also a morphine antagonist (Keats and Telford, 1964a), De Castro and Viars (1968) proposed that it might be used to terminate the respiratory depressant effects of fentanyl.

In their technique "anesthésie analgésique séquentielle", large doses of fentanyl were given to obtund any response to surgery. At the end of the procedure pentazocine was given, also in high dosage. According to the authors, postoperative respiratory depression ceased to be a problem, since the intense effects of fentanyl were substituted by those of a more modest dose of pentazocine. Later, Rifat (1972) described a more conservative technique using smaller doses, and claimed good cardiovascular stability during surgery, effective reversal of respiratory depression, rapid arousal, and excellent control of postoperative pain.

This technique did not enjoy wide favour, partly because the concept of using one agonist to terminate the effects of another seemed both alien and unreasonable to many practising anaesthetists, but also because at that time most clinicians used fentanyl with great caution. It may be said that "anesthésie analgésique séquentielle" was a solution without a problem. Subsequent concern over the incidence of psychotomimetic side-effects following the use of pentazocine (Edison, 1969; Gould, 1972; Wood et al., 1974) ensured that the method remained unpopular. However, recent work has given new insight into the mechanisms involved, and further development of the concept seems possible.

Until recently, the mode of action of opioids has been shrouded in mystery, despite the discovery of a number of distinct receptor populations and an ever-increasing number of endogenous ligands (Martin, 1984). A number of groups have sought to identify the receptor binding characteristics of clinically used opioids, and a fascinating picture has emerged which has far-reaching clinical implications.

It had long been observed that, in the presence of morphine, small doses of nalorphine exerted an antagonistic effect, but paradoxically, the antagonism appeared to diminish with increasing dose. Martin (1967) suggested that this curious interaction could be explained by invoking the concept of *receptor dualism.* He argued that a drug such as nalorphine could exert an agonist effect at one receptor type (kappa), while behaving as a competitive antagonist at another (mu). Thus, in the presence of morphine, nalorphine acts as a competitive mu-antagonist at all doses, but also exerts a low-potency partial agonist effect at the kappa receptor. Pentazocine has been shown to have a similar profile (Gilbert and Martin, 1976), but with strong agonist and weak antagonist properties. The psychotomimetic properties of both agents were ascribed to occupancy of a third (sigma) receptor type.

This theory provides a rationale for sequential anaesthesia, since it may be invisaged that the postoperative dose of pentazocine served to antagonize the mu effects of fentanyl, while exerting a kappa agonist effect to yield effective analgesia. Pentazocine has been reported as causing a less steep depression of the carbon dioxide response curve than morphine (Keats and Telford, 1964b), and it has been suggested that, under some conditions, the curve may be non-linear, reaching a maximal effect plateau after only moderate doses (Engineer and Jennett, 1972).

The oripavine derivative buprenorphine is a partial agonist with long duration of action but low potential for psychotomimetic side-effects or physical dependence (Cowan, Lewis and MacFarlane, 1977). These characteristics raise the intriguing possibility that this agent might be superior to pentazocine in "sequential analgesia". Therefore the receptor binding characteristics, and their interaction with other opioids, are of considerable interest.

Hambrook and Rance (1976) found that buprenorphine differs from all other clinically useful opioids in having very slow receptor kinetics, so that the rate of receptor association and dissociation are likely to be rate limiting for the onset and offset of effect.

The dose–response curve for buprenorphine analgesia (in rats and mice) has been shown to be "bell-shaped", that is, increasing to a peak, then decreasing again towards zero with increasing doses (Cowan, Lewis and Macfarlane, 1977; Dum and Herz, 1981). Moreover, in the latter experiments the time course of analgesia in these animals was biphasic (showing two successive peaks) after large doses, suggesting that not only did analgesia "go over the top" with increasing receptor binding, but also returned to a second peak as occupancy decreased. These experimental findings were difficult to reconcile with early reports that buprenorphine is a selective mu-agonist (Martin et al., 1976), since this precludes the possibility that the form of the dose–response curve is attributable to non-competitive auto-antagonism (i.e. that occupancy of a second, lower affinity receptor type antagonizes, at high biophase concentration, the effect already achieved by occupancy of the first (Ariens, Van Rossum and Simonis, 1957)).

Sadee, Rosenbaum and Herz (1982) showed that, in fact, buprenorphine binds to a population of high-affinity receptors at low doses, but with high doses it binds also to a distinct group of low-affinity sites. With the recent availability of subtype-specific ligands, Villiger (1984) showed that buprenorphine has high affinity for both mu and delta (enkephalin) receptor subtypes, and also a somewhat lower affinity for the kappa subtype. Therefore, it seems likely that the non-linear dose–response curve is, in fact, the result of inhibition by receptors distinct from those causing analgesia.

It must be noted that, in his recent and extensive review, Martin (1984) continues to argue that buprenorphine binds selectively to the mu-receptor, and does not comment on, or attempt to explain the bell-shaped dose–response curve!

Villiger, Ray and Taylor (1983) showed that fentanyl binds selectively to the mu subtype, with both high and low affinities. It seems likely that the high affinity subset corresponds to the mu-1 type identified by Ling and co-workers (1983), the occupancy of which by morphine is responsible for the analgesic but not the respiratory depressant actions of that drug. It is of passing interest that meptazinol has very recently been shown to have high selectivity for the mu-1 receptor type, which is in keeping with the relatively minor effect of the agent upon respiration (Spiegel and Pasternak, 1984).

If buprenorphine is to be used to "switch off" intense fentanyl analgesia, the individual characteristics of the two drugs are not so important as the dynamics of the interaction between them. In this issue, Boas and Villiger (1985) consider this problem in detail with a series of *in vitro* receptor binding studies. Their results and conclusions will stimulate a renewed interest in "anesthésie analgésique séquentielle", and clinical investigators will have a clear understanding of the processes they seek to control.

Whether the bell-shaped dose–response curve for buprenorphine so elegantly demonstrated by Dum, Herz and others has any relevance whatever to our patients, remains to be seen.

C. J. Hull

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ELECTRICAL ACTIVITY OF THE CEREBRAL CORTEX DURING INDUCED HYPOTENSION IN MAN

A Comparison of Sodium Nitroprusside and Trimetaphan

W. A. THOMAS, P. V. COLE, N. J. ETHERINGTON, P. F. PRIOR AND S. B. STEFANSSON

SUMMARY

During the routine use of controlled hypotension the electroencephalogram (EEG) and mean arterial pressure (MAP) were monitored in 20 normotensive patients (younger than 70 years-of-age) receiving either trimetaphan (TMP) or sodium nitroprusside (SNP). The reduction in MAP was quicker and greater with SNP. Significant differences in EEG voltage between the two agents were seen in the range 55–40 mm Hg, electrical activity being better maintained with SNP. However, all patients showed some decline in EEG voltage with hypotension and half of these showed significant correlations with MAP. These pressure-dependent cerebral effects were not predictable in terms of age, preoperative arterial pressure or hypotensive agent. Our work supports previous experimental evidence that, during more profound hypotension, cerebral electrical activity is better maintained with SNP than with TMP. A simple measure of total EEG power, or filtered EEG voltage envelope (CFM) was shown to be a more useful monitor of cerebral electrical activity during controlled hypotension than measurements of power distribution in different frequency bands.

Since the advent of controlled hypotension during anaesthesia and surgery in the 1950s, doubts have been expressed as to the adequacy of the cerebral circulation during the hypotensive period. Critical values of cerebral perfusion pressure (CPP), their correlations with the EEG and evoked potentials, and the pattern of brain damage produced by inadequate CPP were defined in the Rhesus monkey by Brierley and colleagues (1969) and Meldrum and Brierley (1969). There is evidence that cerebral perfusion and oxygen metabolism are better maintained with sodium nitroprusside (SNP) than with trimetaphan (TMP) in the dog (Stoyka and Schutz, 1975; Michenfelder and Theye, 1977) and the cat (Maekawa, McDowall and Okuda, 1979). In 1981, Ishikawa and McDowall confirmed that cerebral blood flow in the cat was greater at low arterial pressures with SNP than with TMP. In addition, they demonstrated a close relationship between the EEG (both assessed visually and processed by the Cerebral Function Monitor (CFM)) and the cortical cerebral blood flow. If these animal models are relevant to man, SNP would seem to be the agent of choice for induced hypotension.

To obtain an objective comparison of SNP and TMP during induced hypotension in man, we designed a controlled, single-blind study, with monitoring of the EEG (primarily by the CFM) to give presumptive evidence of the adequacy of cerebral perfusion. Since no anaesthetic technique used deviated from the standard practice of this hospital, no ethical approval was considered necessary.

PATIENTS AND METHODS

Twenty patients undergoing major orthopaedic, gynaecological and plastic surgical procedures for which induced hypotension was routine practice, were allocated randomly to two groups (table I). One group (mean age 53 ± 10.2 yr) received SNP, and the other (mean age 47 ± 15.3 yr) received TMP. Patients were excluded if they were over 70 years-of-age; their diastolic arterial pressure exceeded

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TABLE I. *Details of patients undergoing surgery and controlled hypotension with sodium nitroprusside (SNP) or trimetaphan (TMP). Data include age, sex, MAP, arterial* Po_2 *and carbon dioxide tensions and duration of hypotension, as well as the arterial pressure at which average CFM voltage became pressure dependent. Significance of differences between mean values for SNP and TMP compared using Student's* t *test*

	Patient no.	Age (yr)	Sex	Pre-op. MAP (mm Hg)	Duration of hypotension (min)	Pa_{CO_2} (kPa)	Pressure-dependent threshold (mm Hg)
SNP	1	31	M	81	70	6.0	66
	2	31	M	117	150	5.6	48
	3	65	F	120	78	5.3	61
	4	25	M	93	100	5.9	*ca* 65
	5	38	F	100	117	4.4	76
	6	68	F	93	43	5.2	70
	7	39	F	97	135	5.2	*ca* 61
	8	61	F	117	58	5.4	66
	9	62	F	97	76	4.8	50
	10	50	F	93	72	4.3	46
Mean		47		101	90	5.2	61
SD		16		13	35	0.6	10
TMP	1	35	F	80	47	5.5	53
	2	42	F	77	65	5.2	65
	3	67	F	107	88	5.7	57
	4	69	F	100	54	5.2	59
	5	53	F	107	76	5.3	*ca* 50
	6	46	F	93	83	5.4	56
	7	60	F	110	72	5.8	41
	8	55	F	100	53	5.0	47
	9	55	M	93	75	5.4	63
	10	48	M	95	82	4.3	48
Mean		53		96	70	5.3	54
SD		11		11	14	0.4	8
P		ns		ns	< 0.01	ns	ns

100 mm Hg before operation; they had historical or clinical evidence of cardiovascular, cerebrovascular, renal or neurological disease.

All the patients were screened by one investigator before operation and premedicated with papaveretum 0.2 mg kg^{-1} and hyoscine 4 µg kg^{-1}. After induction of anaesthesia and tracheal intubation, artificial ventilation (60% nitrous oxide and 0.5% halothane in oxygen) was instituted, neuromuscular blockade being provided by tubocurarine 0.5 mg kg^{-1}. Before surgery, all patients received fentanyl 2–4 µg kg^{-1}. TMP was prepared as a 0.2% solution in 5% dextrose and infused at a rate not exceeding 10 mg kg^{-1} h^{-1} with an automatic infusion controller. SNP 0.01% in 5% dextrose was infused at a rate so as not to exceed a total dose of 1.5 mg kg^{-1} (Cole, 1978). Propranolol in 1-mg increments was administered if the mean arterial pressure (MAP) failed to reach the target value of 40 mm Hg with the maximum dose rate of hypotensive agent, or if the patient developed a tachycardia, defined as a heart rate greater than 80 beat min^{-1}.

MAP and end-tidal carbon dioxide concentration were displayed continually and recorded, on a chart recorder and a Racal "Store 4" tape recorder. Sterile intradermal EEG needle electrodes were placed in the left and right parietal regions, overlying the arterial boundary zones, with a third "guard" electrode in the mid-frontal region. The electrode sites were standardized by the use of a plastic template. The EEG signal was processed and displayed by a CFM on a polygraphic chart and both raw and processed signals stored on the tape recorder. Intermittent blood samples were taken to confirm normal alveolar ventilation, and to ensure adequate oxygenation and absence of metabolic acidosis.

The chart and tape recordings were marked with a numerical code for timing of events such as drug administration. They were analysed blind by two investigators not involved in the acquisition of the data.

Measurements were made manually of MAP and simultaneous average and minimum CFM voltage from the start of the administration of the hypotensive agent until arterial pressure had returned to a steady value once the drug had been discontinued.

The measurements were made at 10-s intervals during the initial decrease in arterial pressure towards the target value, and then at 50-s intervals during the remaining period of hypotension and the final increase in pressure. All CFM measurements were made in mm above the zero μV baseline. This represents the logarithmic transformation of the voltage information and gives a Gaussian distribution of data for statistical processing. They were subsequently converted to equivalent μV values. Each measurement was normalized by expression as a percentage of the mean of the three consecutive 50-s interval values immediately preceding the induction of hypotension. Measurements of minimum CFM value proved to have no advantage over average values and are not referred to further.

A replay of tape recordings of raw EEG signals permitted subsequent visual and automated assessment of alterations in frequency and voltage. Assessment of frequency information was based on visual inspection of the raw EEG traces and of analogue displays of the outputs of high-order Chebyshev filters (Etherington, 1981), the modified CFM, the CFAM (Maynard and Jenkinson, 1984) and fast Fourier transform data (Matoušek, Arvidsson and Friberg, 1978; Matoušek and Petersén, 1983; Matoušek et al., 1985).

RESULTS

Mean arterial pressure decreased more slowly and reached the target value less often with TMP, whereas with SNP the decrease was rapid and sometimes overshot the target. The durations of hypotension and the mean decreases and the rates of decrease in MAP for patients receiving SNP and TMP, are presented in tables I and II. Expressed as percentages, the mean decreases in MAP were 37% and 51% for TMP and SNP, respectively.

Throughout the hypotensive period all patients appeared adequately perfused, with warm, pink extremities. Because of tachycardia or difficulty in achieving the target value of hypotension, 11 patients required β-blockade with propranolol: six of those receiving TMP and five of those receiving SNP.

In all 20 patients the average CFM voltage decreased during the initial reduction in arterial pressure. The decreases in mean voltage and the rates of decrease of the average CFM voltage for the two agents are given in table II. These represent mean decreases of 26% and 25% for patients receiving TMP and SNP, respectively. Thus, the decrease in CFM voltage was similar for the two agents in spite of a much greater decrease in MAP with SNP. No neurological or other sequelae were observed in any patient during the period immediately after operation.

There was a highly significant correlation between MAP and average CFM voltage during the initial reduction in arterial pressure in 10 out of the 20 patients regardless of agent, previous arterial pressure or age (tables I and II). When rates of decrease in arterial pressure were lower, there was a tendency to lower correlation coefficients between MAP and average CFM values.

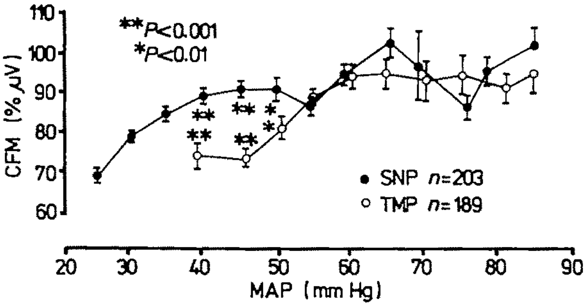

FIG 1 Group means ±1 SEM of values of MAP and average CFM voltage for 10 patients receiving each agent based on 10-s measurements during the initial decrease in MAP towards target value. CFM values expressed as percentage of values before hypotension. Significant differences in mean CFM values between TMP and SNP are present at three values of arterial pressure

When the data, measured at 10-s intervals during the initial reduction in arterial pressure, are grouped according to agent, a significant difference in the relationship between average CFM value and MAP occurs at pressures in the range 55–40 mm Hg (fig. 1). At MAP values less than 40 mm Hg, there were no data for patients receiving TMP. However, with SNP a progressive decrease in CFM voltage occurred.

In every patient an approximate MAP threshold could be identified from plots of all MAP and CFM voltage data throughout the period of hypotension, below which a pressure-dependent decrease in CFM voltage occurred (fig. 2, table I). The mean value was 57.4 ± 9.3 mm Hg. There was no relationship

TABLE II. *Profile of controlled hypotension in each patient, together with observed changes in CFM for both sodium nitroprusside (SNP) and trimetaphan (TMP) groups. Correlation coefficients between MAP and average CFM voltage are based on 10-s measurements during the decrease in MAP from values immediately before hypotension to the end of the initial rapid decrease induced by the hypotensive agent, and from 50-s measurements for the full period of administration of hypotensive agents. Significance of differences between mean values for SNP and TMP compared with Student's* t *test:* *P < *0.01;* **P < *0.001*

	Decrease in MAP			Decrease in average CFM		Correlation coefficients MAP *v.* CFM			
Patient no.	Actual (mm Hg)	Time (min)	Rate (mm Hg min^{-1})	Actual (μV)	Rate (μV min^{-1})	Initial decrease	(*n*)	Full period	(*n*)
SNP 1	95→50	3.7	12.2	10.0→8.5	0.41	−0.108	(16)	0.798**	(78)
2	67→33	10.0	3.4	8.0→6 8	0.12	0.237	(23)	0.599**	(68)
3	50→27	3.0	7.7	8.5→6.1	0.8	0.846**	(25)	0.334**	(94)
4	68→40	2.5	11.2	8.0→6.1	0.76	0.838**	(17)	0.453**	(97)
5	78→25	3.3	16.1	6.5→5.1	0.42	0.633**	(33)	0.080	(60)
6	68→28	2.8	14.1	13.0→8.5	1.61	0.835**	(21)	0.454**	(49)
7	78→27	1.8	28.1	6.1→4.7	0.78	0.705*	(13)	0.264	(65)
8	85→45	4.0	10.0	12.0→8.0	1.0	0.476	(23)	0.470**	(68)
9	43→32	2.3	4.9	6.8→5.8	0.44	0.410	(13)	0.326*	(84)
10	56→24	3.0	10.7	8.0→4.7	1.10	0.814**	(21)	0.655**	(78)
Mean	69→33	3.6	11.8	8.7→6.4	0.74	0.569	(20.5)	0.443	(74.1)
SD	16→9	2.3	6.9	2.3→1.5	0.43	0.317	(6.1)	0.207	(15.0)
TMP 1	65→47	12.5	1.4	6.1→4.0	0.17	0.940**	(15)	0.677**	(48)
2	76→48	25.0	1.1	6.1→4.7	0.06	0.656*	(21)	0.282	(69)
3	76→44	6.3	5.1	12.0→8.5	0.56	0.668	(11)	0.319*	(93)
4	85→45	4.0	10.0	9.5→7.5	0.50	0.381	(24)	0.763**	(60)
5	50→40	2.5	4.0	5.1→2.4	1.08	0.952**	(15)	0.293*	(92)
6	64→47	4.0	4.3	8.5→6.1	0.60	0.723**	(32)	0.160	(86)
7	62→35	5.0	5.4	8.5→8.0	0.20	−0.217	(10)	0.202	(84)
8	87→40	4.0	11.8	7.2→6.1	0.28	0.459	(18)	0.598**	(49)
9	75→43	21.0	1.6	6.5→4.0	0.11	0.027	(22)	0.427**	(68)
10	54→38	7.0	2.3	8.0→6.8	0.17	0.444	(24)	0.117	(96)
Mean	69→43	9.1	4.7	7.8→5.8	0.37	0.503	(19.2)	0.384	(74.5)
SD	12→4	7.9	3.6	2.0→2.0	0.31	0.373	(6.7)	0.225	(18.2)
P	<0.01	<0.05	<0.01	ns	<0.05	ns		ns	

to age or to arterial pressure before operation. When the mean values for patients receiving TMP (54 ± 7.5 mm Hg) and for those receiving SNP (61 ± 9.94 mm Hg) were compared, a trend emerged, but did not reach statistical significance.

As the amplitude of the CFM trace decreased (by a mean of 26%), the raw EEG, the Chebyshev filter outputs and the Fourier frequency analyses showed fairly consistent decreases in amplitude in all frequency bands. Comparing activity immediately before hypotension with that when the initial decrease in arterial pressure was complete, significant changes ($P < 0.05$ on Student's t tests) were seen in several variables in all patients. The significant alterations from the Fourier analysis all concerned amplitudes (square roots of power). Expressed as mean percentages in order of severity, these were: amplitude in the upper alpha (10–12.5 Hz) band, 25% decrease; amplitude in delta (1.5–3.5 Hz) band, 23% decrease; amplitudes in lower alpha (8–9.5 Hz) and lower beta (13–17 Hz) bands, both 18% decrease; sum of all amplitudes (1.5–25 Hz), 17% decrease. In all patients there were significant decreases in the sum of all the Fourier amplitudes in the 1.5–25 Hz range and the five CFAM amplitude measures (maximum, 90th centile, mean, 10th centile and minimum amplitudes). The significant changes in the other Fourier variables listed above occurred in the majority of patients, but were not universal. There were no significant alterations in frequency distribution, expressed as percentage of power in each band, in any patient. Frequency ratios, that is, of slow:fast EEG activity [(theta+delta)/(alpha+beta)] showed significant alterations (either an increase or a decrease) in only a minority of patients.

Significant correlations were shown between MAP and EEG measurements taken at 10-s intervals during the acute decrease in arterial pressure. The CFM showed the highest correlation with MAP (table

II), but also significant ($P < 0.05$) were the correlations between MAP and delta, upper alpha and lower beta amplitudes (correlation coefficients each 0.36) and lower alpha and theta amplitudes (correlation coefficients 0.22 and 0.18, respectively). Bearing in mind the loss of information as a result of occurrence of slow-wave artefact in recordings from the operating theatre, the amplitudes in the range 10–17 Hz appear to give the most reliable correlations with decreasing arterial pressure.

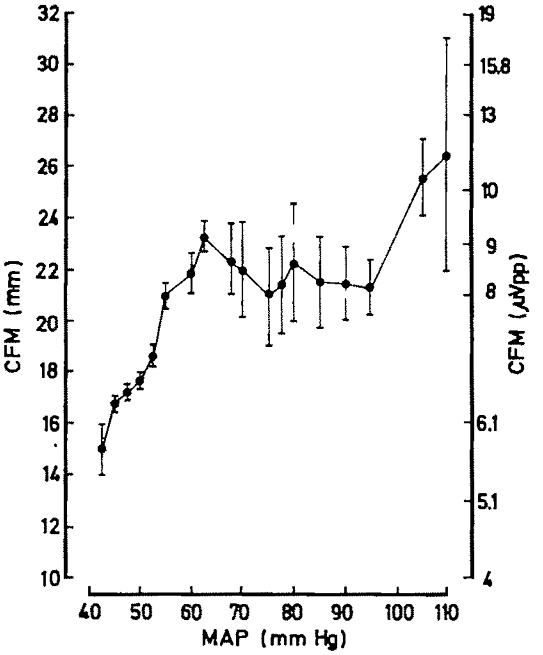

FIG 2. A 31-year-old normotensive male during lumbar laminectomy with controlled hypotension induced by sodium nitroprusside (SNP). Smoothed (three-point running average) means ±1 SEM of all MAP and average CFM voltage values ($n = 102$) in each 5-mm Hg range from measurements at 50-s intervals throughout the operation. In this patient it was particularly notable that the CFM voltage decreased and became less variable, that is, the standard errors diminished, in relation to decreasing MAP below about 60–65 mm Hg

DISCUSSION

We have shown that, in man, a decrease in MAP within the usual clinical range of controlled hypotension is reflected consistently in a decrease in cortical electrical activity (EEG). Furthermore, at mean arterial pressures between 55 and 40 mm Hg, the degree of depression is significantly greater with TMP than with SNP. These findings are in keeping with experimental evidence, particularly that of Ishikawa and McDowall (1981). These authors showed that, at low MAP, cerebral blood flow was better maintained with SNP than with TMP. They also demonstrated the close correlation between the EEG ("power" being measured by the CFM) and cerebral blood flow during induced hypotension in the cat. This validated the use of EEG as a non-invasive indicator of the adequacy of blood flow or oxygenation in these circumstances.

The EEG changes began at a mean arterial pressure threshold of 57 mm Hg, close to that at which autoregulation of cerebral blood flow normally fails (Lassen, 1959; Oleson, 1973). The high correlation between decrease in average CFM voltage and MAP, which occurred in half the patients, does not appear to be predictable in terms of expected risk factors. The efficiency of the mechanisms governing autoregulation depends on the method used to induce hypotension and on its rate of administration (Fitch et al., 1976), on the previous arterial pressure (Strandgaard et al., 1973; Strandgaard, 1976; Fitch et al., 1978), the age of the subject (Hoffman, Albrecht and Miletich, 1982) and the rate of decrease in arterial pressure (Patel, 1981). In our relatively small series of patients, we were unable to show any effects of either age or preoperative MAP. Both younger and older individuals appeared equally likely to show a strong correlation between decreasing arterial pressure and declining cortical electrical activity, whether the rate of decrease was in the higher range produced by SNP or the lower range produced by TMP. It should be borne in mind that we had excluded patients who were older than 70 yr or had previous hypertension or evidence or cerebrovascular disease. However, the implication must be that all patients, regardless of age, previous arterial pressure etc., are at risk from increasing cerebral oligaemia when their MAP is reduced below the value at which a decrease in EEG voltage begins.

Cerebral oligaemia, whatever its cause, leads to brain damage of a characteristic arterial boundary zone distribution (Graham, 1977; Brierley et al., 1980). This pattern of cerebral infarction occurs in the Rhesus monkey when oligaemia during profound hypotension has resulted in at least 15 min EEG silence (Brierley et al., 1969). Shorter periods of electrical silence were shown to be completely reversible without cerebral damage when adequate circulation was restored. This is the basis of the so-called dual threshold for cerebral ischaemia (Astrup et al., 1977; Morawetz et al., 1979), whereby the initial extinction of spontaneous or evoked electrical activity has to be sustained by continuous or increasing ischaemia for a finite period before irreversible neuronal damage occurs. Thus, the EEG provides a relevant monitor of neuronal function, since a decrease in voltage gives warning of cerebral oligaemia before ischaemic damage would occur. It is not yet known how long it takes to produce cerebral infarction in man when induced hypotension has resulted in a reduction in cerebral blood flow sufficient to produce electrical silence. However, it is likely to take less time than in the young healthy experimental animals studied by Brierley and colleagues (1969). Indeed, evidence from studies of ischaemic brain damage of a similar arterial boundary zone distribution, following cardiac surgery, suggests that a period of about 7 min major depression of EEG must occur before infarction ensues (Malone, Prior and Scholtz, 1981).

The MAP threshold at which a pressure-dependent effect begins to occur is of interest. This is at a slightly higher pressure with SNP and probably merely relates to the moment of onset of maximal cerebral arteriolar vasodilatation, which leads to inactivation of the autoregulatory capacity. However, as McDowall (1982) has pointed out, it is incorrect to speak of autoregulation of cerebral blood flow under the particular conditions of hypotension induced by SNP. This cerebral vasodilatation presumably occurs concurrently with dilatation of the systemic vascular bed and the consequent reduction in arterial pressure. Despite this, cerebral perfusion may actually increase as a result of an increased cardiac output with SNP (Wildsmith et al., 1973; Pickard et al., 1981). This contrasts sharply with the case of TMP where the cardiac output is decreased (Jordan et al., 1971) and, given that autoregulation is in abeyance at these low pressures, this means reduced cerebral blood flow. There is, indeed, evidence from our work in man that there is better maintenance of cerebral electrical activity with SNP than TMP at similar values of hypotension. However, it was possible to detect the onset of an alteration in the relationship between average CFM value and MAP, even though it was rarely as dramatic as in the patient illustrated in figure 2. The evidence arising from the frequent need to use β-blockade to control tachycardia suggests continuing sympathetic activity in patients receiving both agents. It is surprising that a ganglion blocking drug such as TMP did not obliterate this phenomenon.

Differences in the degree of correlation between MAP and average CFM voltage were apparent when the 10-s measurements during the initial decrease in arterial pressure were compared with the 50-s measurements during the whole period of hypotension in individual patients. In all patients surgical stimulation tended to increase after the initial reduction in arterial pressure had been achieved. This, given the generally light level of anaesthesia, tended to lead to more variable traces and obscure the simple relationship between arterial pressure and EEG. Furthermore, in patients receiving sodium nitroprusside the initial decrease was achieved over a relatively short period, limiting the number of measurements obtainable and, thus, the possibility of achieving significant correlation; these patients also tended to have longer periods of hypotension (90 min on average, compared with 70 min for patients receiving trimetaphan) with a greater possibility of other factors affecting the EEG as a consequence. This may explain our inability to show a significant difference between the two drugs when measurements during the whole period of hypotension were included.

The automatic frequency analysis supported the evidence from the CFM traces. There was a consistent decrease in the summed amplitudes from each of the traditional EEG frequency bands and most significantly in the delta, upper alpha and lower beta ranges as MAP decreased towards target values. This contrasted with the infrequent and inconsistent alterations in the percentage of total activity falling in each frequency band which rendered indices such as slow:fast frequency ratios and mean frequency ineffective. The relatively light level of anaesthesia in our patients contrasts with that in many of the earlier experimental studies where decreases in faster and increases in slower EEG frequencies were reported as evidence of impending cerebral ischaemia (Sugar and Gerard, 1938; Gibbs, Williams and Gibbs, 1940). Thus, frequency analysis of the EEG provided inconsistent changes during hypotension and offered no advantage over the CFM recording.

Patients are monitored during induced hypotension to reduce unnecessary risks. Clearly, guarding against unexpected or exceptional decreases in MAP by intra-arterial pressure monitoring has proved of major importance in this respect. However, it is quite unpredictable in which patients the cerebral circulation is unable to tolerate reductions in MAP to less than about 60 mm Hg. This implies that direct cerebral monitoring is mandatory, should it become necessary to decrease arterial pressure below this value. The methods need to be simple but effective. This study has demonstrated that a suitable measure is total EEG power or the amplitude envelope of filtered EEG as provided by the CFM.

The evidence from the present study also raises the question as to whether decreases in arterial pressure to less than a mean of 60 mm Hg are ever justified during routine surgery. The question is reinforced by reports that a decrease in blood loss is achieved mainly by quite modest decrease of arterial pressure and that greater hypotension does not produce greater benefit (Donald, 1982). Our evidence also supports that of Stoyka and Schutz (1975), Michenfelder and Theye (1977), Maekawa, McDowall and Okuda (1979) and Ishikawa and McDowall (1981) that, if even greater hypotension is required, sodium nitroprusside is the agent of choice to ensure the safety of the brain.

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USE OF NITROGLYCERINE TO PRODUCE CONTROLLED DECREASES IN MEAN ARTERIAL PRESSURE TO LESS THAN 50 MM HG

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SUMMARY

The cardiovascular effects of nitroglycerine (TNG) were studied in 30 patients requiring controlled hypotension for intracranial aneurysm surgery. In patients "resistant" to TNG (n = 9), sodium nitroprusside (SNP) was used to supplement the TNG. With TNG alone at a total dose of 31 mg and a mean hypotension duration of 28 min, mean arterial pressure (MAP) decreased by 43%, from 78.3 to 44.4 mm Hg as a result of decreases in cardiac index (CI) (18%) and systemic vascular resistances (SVR) (21%). Simultaneously, a moderate increase in ($Ca_{O_2} - Cv_{O_2}$) (21%), and a significant increase in plasma renin activity (90%) were observed. In patients "sensitive" to TNG, the MAP decreased by 54%, CI by 27% and SVR by 35%; HR remained stable. In patients "resistant" to TNG, the decreases in CI and SVR were less marked: 2% and 22% respectively; the observed increase in HR was 12%. When non-toxic doses of SNP were used ($< 2\ \mu g\ kg^{-1}\ min^{-1}$), hypotension was caused by decreased SVR (31%) and increased CI (8%). TNG alone can be used to produce controlled decreases in MAP to around 50 mm Hg, and in patients "resistant" to TNG, SNP can be added to increase the hypotensive effect.

Controlled hypotension is used frequently during intracranial aneurysm surgery, since it decreases both the risk of rupture of the aneurysm, and the mortality rate attributable to this type of surgery (Viars et al., 1976). However, the choice of technique and the ideal arterial pressure remain controversial. The ideal arterial pressure varies from 60 mm Hg to less than 40 mm Hg (Pertuiset et al., 1974; Chestnut et al., 1978), although the value quoted most frequently is 50 mm Hg.

Ganglionic blocking drugs and halothane are used less frequently than in the past. Sodium nitroprusside (SNP), introduced by Moraca and colleagues (1962), has been used widely because of its ability to induce rapid, reversible hypotension. However, it is known that this drug has certain potentially harmful side-effects, so that nitroglycerine (TNG) has been considered seriously by certain workers (Fahmy, 1978). Nitroglycerine is a non-toxic vasodilator which easily induces moderate hypotension. However, the question remains whether this drug can be used for hypotension equal to or greater than 50 mm Hg, and certain authors have noted that this value cannot be obtained without supplementation. Numerous studies have recorded the haemodynamic effects of TNG alone (Chestnut et al., 1978; Urcioli et al., 1980; Lagerkranser, 1982) but not with adjuvant drugs and not under general anaesthesia.

The aims of this study were first to determine whether TNG used alone (in association with general anaesthesia) could decrease arterial pressure to less than 50 mm Hg and, second, if this failed, whether SNP could be used to supplement the action of TNG to obtain the desired hypotension.

PATIENTS AND METHODS

Patients

After all patients had given informed consent and the experimental programme had been approved by the hospital ethics committee, 30 patients (14 female) were studied. Their average age was

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40 ± 13yr (mean ± SD) and their mean weight 63.9 ± 12.9 kg (mean ± SD). All patients had a ruptured intracranial aneurysm and were in Grades I or II (Hunt and Hess, 1968). None had clinical evidence of cardiac insufficiency.

General anaesthesia

Premedication consisted of sublingual diazepam 10 mg. After an injection of atropine 0.5 mg i.v., thiopentone 5 mg kg^{-1} was administered. This was followed by suxamethonium 1 mg kg^{-1} to facilitate tracheal intubation. Anaesthesia was maintained with repeated doses of phenoperidine (total dose 7.72 ± 1.24 mg (mean ± SD)) and droperidol (total dose 39.8 ± 11.8 mg (mean ± SD)), and a mixture of 60% nitrous oxide in oxygen. Ventilation was controlled to maintain $Pa\text{CO}_2$ between 4 and 4.8 kPa. All patients were operated in the supine position. Mannitol 0.5 mg kg^{-1} was administered to three patients before the induction of deliberate hypotension.

Controlled hypotension

Hypotension was induced with an infusion i.v. of TNG in propylene glycol solution 45 mg in 30 ml using a polypropylene syringe, and polyethylene tubing. The infusion was started during the dissection of the aneurysm and discontinued after successful ligation. The infusion rate was adjusted to achieve the desired value of arterial pressure (less than 50 mm Hg). When it was possible to attain the intended mean arterial pressure (MAP) (50 mm Hg) the patients were called "sensitive" and when this value was unobtainable, despite what was considered a maximum TNG infusion rate, patients were called "resistant". In those "resistant" patients in whom it appeared essential to decrease MAP to less than 50mm Hg, SNP 0.5–2 μg kg^{-1} min^{-1} was administered via another vein, in addition to the TNG, which was maintained at the same maximum flow of 30 μg kg^{-1} min^{-1}.

Haemodynamic measurements

A cannula was inserted to the radial artery and arterial pressure measured. Following the induction of anaesthesia, a 7F flow-directed catheter was inserted and advanced until its tip wedged in a small branch of the pulmonary artery. Right atrial pressure (RAP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP) were recorded continuously on a multichannel recorder (Hewlett–Packard). Cardiac output (CO) was determined in triplicate, using the thermodilution technique (Hewlett-Packard) and the mean value was used. Heart rate (HR) was recorded continuously (Hewlett-Packard). Cardiac index (CI) was calculated using the formula:

$$\text{CI} = \frac{\text{CO}}{\text{Body surface}} \ (\text{litre min}^{-1}\ \text{m}^{-2})$$

Stroke volume (SV) was calculated using the formula:

$$\text{SV} = \frac{\text{CI} \times 1000}{\text{HR}} \ (\text{ml m}^{-2})$$

Systemic vascular resistance (SVR) was calculated using the formula:

$$\text{SVR} = \frac{\text{MAP} - \text{RAP}}{\text{CI}} \ (\text{kPa litre}^{-1}\ \text{min}^{-1}\ \text{m}^{-2})$$

Pulmonary vascular resistance (PVR) was calculated using the formula:

$$\text{PVR} = \frac{\text{PAP} - \text{PCWP}}{\text{CI}} \ (\text{kPa litre}^{-1}\ \text{min}^{-1}\ \text{m}^{-2})$$

Measurement times

In all patients ($n = 30$), haemodynamic measurements were obtained before the induction of deliberate hypotension (T_1), at the time of maximum hypotension with TNG alone (T_2) and 30 min after the discontinuation of the drug infusion (T_3). In certain patients ($n = 7$) haemodynamic data were recorded at an intermediary stage—around 50 mm Hg. When SNP was administered, haemodynamic measurements were taken once the maximum degree of hypotension had been achieved.

Blood analyses

In 19 patients, arterial and mixed venous blood-gas tensions were measured at T_1 and T_2. Arterio–venous oxygen content difference ($Ca\text{O}_2 - Cv\text{O}_2$) and total oxygen uptake ($V\text{O}_2$) were calculated using standard formulae. Blood samples were taken in all 30 patients at T_1, T_2 and T_3 and plasma renin activity (PRA) measured.

The data presented are mean values ± the standard deviation (SD) or the standard error of the mean (SEM) and include first, the overall values when the most profound degree of hypotension had been obtained with TNG alone ($n = 30$); second, a comparison between values obtained in the "sensitive" group and the "resistant" group; and third, values obtained in "resistant" patients once SNP had been administered.

The statistical significance of the results was determined using the Student's t test for paired and unpaired data. The correlation r was the coefficient used to identify the significance of the linear regression; $P < 0.05$ was considered significant.

RESULTS

Hypotension was achieved rapidly in 4–5 min following the administration of TNG and maintained for about 30 min. Following discontinuation MAP returned to pre-induction values and with no rebound effect (fig. 1).

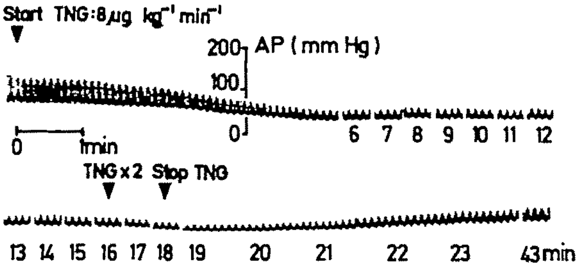

FIG 1. Example of hypotension with TNG from one patient.

The general characteristics of all the patients, both "sensitive" and "resistant", under controlled hypotension are shown in table I.

All patients

The results obtained for all patients are presented in table II: MAP decreased by 43% and PAP decreased by 48%. These results are related to a decrease both in CI (18%) and in peripheral resistances (SVR 30%, PVR 21%). A significant linear relation ($P < 0.001$) existed between the decrease in CI as a percentage and that of MAP: $\%MAP = 0.58\ \%CI - 33$, $r = 0.67$. The greatest decrease in CI was 58% for an MAP of 26.3 mm Hg. HR increased moderately (7%) although there were variations (seven instances of sino-bradycardia < 50 beat min^{-1} at maximum hypotension) between individuals.

The mean increase in PRA of 90% was significant. Blood-gas tensions showed a moderate increase in ($Ca_{O_2} - C\bar{v}_{O_2}$) from 33 ± 3 to 40 ± 4 vol $litre^{-1}$, whereas $\dot{V}_{O_2}$ was not statistically modified, Pa_{O_2} decreased from 22.3 ± 1.6 to 16.1 ± 1.7 kPa ($P < 0.05$) accompanied by an increase in venous admixture from 11.7 ± 2% to 15.9 ± 2.5% ($P < 0.05$).

Comparison of "sensitive" and "resistant" patients

The mean value of MAP was 44.4 mm Hg for the whole group of 30 patients, but in 11 patients we were unable to achieve an MAP of less than 50 mm Hg. The "resistant" group differed from the "sensitive" group (table III), in that decreases in CI (2% compared with 27%) and SVR (22% compared with 35%) were less marked, whereas the increase in HR (12% compared with 3%) was greater. These differences disappear, however, if we consider comparable arterial pressures in both "resistant" (table III) and "sensitive" patients (table IV). In this case and for MAP between 50 and 60 mm Hg, the increase in HR was identical (12%) and no significant difference in CI was observed between the two groups. The three patients who received mannitol were all in the "sensitive" group.

Combination of TNG + SNP

In nine of the 11 "resistant" patients, arterial pressure had to be deliberately decreased below 50 mm Hg (table V). When MAP was decreased another 31%, CI and HR increased slightly (CI 8%, HR 11%).

DISCUSSION

The results suggest that TNG can be administered to patients under general anaesthesia and controlled ventilation to obtain controlled decreases in arterial

TABLE I. *Characteristics of all patients* (n = *30*), *of the "sensitive" patients* (n = *19*), *and of the "resistant" patients* (n = *11*). *Values are mean* ± *SD.* *P < *0.05* v. *"sensitive" patients*

	Sex ratio	Age (yr)	Body weight (kg)	Hypotension time (min)	Dose of TNG (mg)
All patients	14F:16M	40 ± 12.9	63.9 ± 9.2	28 ± 16	31 ± 27
"Sensitive" patients	9F:10M	42 ± 12.8	62.9 ± 8.3	27 ± 14	20 ± 10
"Resistant" patients	5F:6M	35 ± 12.3	65.6 ± 11.1	30 ± 19	35 ± 16*

TABLE II. *Haemodynamic data and PRA concentrations (mean values ± SEM) in 30 patients under general anaesthesia using TNG alone, before* (T_1) *during* (T_2) *and 30 min after discontinuation of drug infusion* (T_3). $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ *compared with* T_1

	T_1	T_2	T_3
MAP (mm Hg)	78.30 ± 2.40	44.43 ± 2.59***	71.90 ± 2.26*
HR (beat min^{-1})	61 ± 2.35	65 ± 3.66	66 ± 3.54
CI (litre min^{-1} m^{-2})	3.04 ± 0.14	2.49 ± 0.12**	2.88 ± 0.12
SV (ml m^{-2})	51 ± 1.90	40 ± 2.2***	46 ± 2.3*
SVR (kPa litre^{-1} min^{-1}m^{-2})	3.44 ± 0.19	2.41 ± 0.16**	3.38 ± 0.20
RAP (mm Hg)	3.72 ± 0.40	1.14 ± 0.34***	2.92 ± 0.44*
PAP (mm Hg)	11.23 ± 0.66	5.87 ± 0.36**	9.17 ± 0.67**
PCWP (mm Hg)	5.42 ± 0.50	2.07 ± 0.35***	3.72 ± 0.55**
PVR (kPa litre^{-1} min^{-1} m^{-2})	0.27 ± 0.03	0.22 ± 0.02*	0.28 ± 0.04
PRA (µg ml^{-1} h^{-1})	5.98 ± 0.89	11.41 ± 2.13**	10.35 ± 1.36*

pressure to around 50 mm Hg. The decrease in MAP was achieved by the vasodilatory effect of TNG on arterial and venous vessels (Cyong et al., 1976; Vatner et al., 1978). Venous return decreased, as shown by decreased filling pressures (RAP and PCWP) and a decrease in SI. The result was a decrease in SVR (30%) and CI (Lagerkranser, 1982). On average, this decrease in CI was moderate (18%) but depended on the ultimate value of MAP (correlation between MAP and CI). Compared with nitroprusside, with which there are biphasic changes in CI (Stoyka and Schutz, 1975), CI does not increase in the case of moderate MAP (50 – 60 mm Hg) with TNG, possibly as a result of the very slight increase in HR. Nevertheless, in one-third of the patients, TNG used alone was inadequate to achieve hypotension of less than 50 mm Hg.

In "sensitive" patients MAP 35 mm Hg was obtained using doses of TNG 0.8 mg min^{-1} (at a rate of 5–20 µg kg^{-1} min^{-1}). This decrease in MAP was, as in all the patients, the result of decreases in SVR and CI. As for moderate values of MAP, HR increased significantly, but this was insufficient to counterbalance the effects of the decreases in SVR and venous return on CI (Lagerkranser, 1982). At

TABLE III. *Comparison of "sensitive" and "resistant" patients, after administration of TNG alone and in seven "sensitive" patients in whom MAP was around 50 mm Hg. Values are mean ± SEM.* $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ *compared with control value.* $^\dagger P < 0.05$; $^{\dagger\dagger\dagger}P < 0.001$ *compared with "resistant" patients at* T_2

	"Resistant" patients ($n = 11$)	"Sensitive" patients ($n = 19$)	"Sensitive" patients MAP 50 mm Hg ($n = 7$)
MAP (mm Hg)			
T_1	80.2 ±4.9	77.2 ±2.7	50.3 ±0.9**†
T_2	59.8 ±2.7***	35.5 ±1.6***†††	
HR (beat min^{-1})			
T_1	62 ±4	60 ±3	64 ±6**
T_2	69 ±5*	62 ±4	
CI (litre min^{-1} m^{-2})			
T_1	2.92 ±0.16	3.11 ±0.20	2.45 ±0.24
T_2	2.86 ±0.16	2.27 ±0.15***	
SVR (kPa litre^{-1} min^{-1} m^{-2})			
T_1	3.65 ±0.42	3.32 ±0.19	2.86 ±0.29*
T_2	2.84 ±0.29**	2.19 ±0.19***†	
PRA (µg ml^{-1} h^{-1})			
T_1	5.74 ±1.34	6.5 ±1.2	
T_2	12.1 ±3.3	10 ±1.9	
TNG (mg min^{-1})	1.2 ±0.06	0.8 ±0.02†	

TABLE IV. *Changes in mean arterial pressure (MAP), heart rate (HR), cardiac index (CI) and systemic vascular resistances (SVR) in seven patients with haemodynamic data at around MAP = 50 mm Hg (mean values ± SEM).* $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ *compared with* T_1 $^{\dagger}P < 0.05$ *compared with MAP = 50 mm Hg*

	T_1	MAP 50 mm Hg	T_2
MAP (mm Hg)	72.9 ± 4.1	50.30 ± 0.94**	37.70 ± 2.6**†
HR (beat min^{-1})	56.80 ± 5.1	64 ± 6**	57.40 ± 6.6
CI (litre min^{-1} m^{-2})	2.82 ± 0.22	2 45 ± 0.24	2.13 ± 0.18*†
SVR (kPa $litre^{-1}$ min^{-1} m^{-2})	3.42 ± 0.13	2.86 ± 0.29*	2.43 ± 0.19***†

low values of MAP, bradycardia was observed, probably secondary to an effect of TNG on the baroreflex (Come and Pitt, 1976). Till now, no satisfactory explanation has been given of this phenomenon in "resistant" patients. Several hypotheses can be proposed:

First, the dose of TNG used. In our study doses were higher in "resistant" patients (up to 30 μg kg^{-1} min^{-1}). We considered this to be the maximum dose, because efficacy at higher doses had not been demonstrated, and we wished to avoid the risk of secondary haemoglobinuria from an overdose of propylene glycol (Brittain and D'Arcy, 1962). Before the study, two cases of transitory haemoglobinuria were noted after administration of doses of more than 30 μg kg^{-1} min^{-1}). Tannières and colleagues (1979) could not achieve hypotension of 50 mm Hg even after using TNG 50 μg kg^{-1} min^{-1}. Nevertheless, their anaesthetic was different: notably the fact that droperidol was not used, or was used at smaller doses (0.26 mg kg^{-1}).

Second, there could be alterations in circulating hormone concentrations. However, PRA (at T_1 and T_2) was not different between "sensitive" and "resistant" patients, despite the fact that with SNP a relationship exists between resistance to the drug and increases in PRA concentration (Lienhart et al., 1979).

Third, a different haemodynamic behaviour could be involved. When comparing "resistant" and "sensitive" patients at a comparable value of MAP between 50 and 60 mm Hg, the results were identical, particularly the decreases in CI and SVR, and the increase in HR. The fact that HR then decreased in "sensitive" patients at low values of MAP cannot be considered a significant difference since, at T_2, HR in the two groups was not significantly different and, in addition, in the sensitive group the decrease in HR between MAP = 50 mm Hg and T_2 was not significant.

In resistant patients the addition of small doses of SNP was effective and tolerated well, since CI was increased rather than decreased. The doses of SNP (< 2 μg kg^{-1} min^{-1}) were well below the toxic level (Ivankovich et al., 1983).

TNG would appear to be free of metabolic side-effects (Lagerkranser, 1982) because the decrease in CI is combined with an increase in ($CaO_2 - CvO_2$) without changes in VO_2. Compared with SNP, no post-hypotensive rebound effect was observed and this fact could possibly be associated with a more moderate increase in PRA during hypotension with TNG, than with SNP (Lienhart et al., 1979).

In summary, TNG induced rapid, stable and reversible hypotension (Chestnut et al., 1978) to around 50 mm Hg, but was accompanied by a

TABLE V. *Haemodynamic data (mean values ± SEM) in nine patients using TNG + SNP.* T_1 *= before hypotension;* T_2 *= hypotension using TNG alone,* T_3 *= 30 min after discontinuation of drugs infusion.* $^{*}P < 0.05$; $^{**}P < 0\ 01$ *compared with* T_2

	MAP (mm Hg)	HR (beat min^{-1})	CI (litre min^{-1} m^{-2})	SVR (kPa $litre^{-1}$ min^{-1} m^{-2})	RAP (mm Hg)	PAP (mm Hg)	PCWP (mm Hg)
T_1	82.5 ±5.8	62.3 ±3.8	3.04 ±0.22	3.71 ±0.53	3.5 ±0.5	10.2 ±0 9	5.1 ±1.1
T_2	55.1 ±4.9	64 ±3.8	2.76 ±0 22	2 78 ±0.44	0.9 ±1	5.9 ±0.5	1.8 ±0 5
TNG + SNP	38 ±2.6**	71 ±4.6*	2.97 ±0.50	1.92 ±0.29*	0.9 ±0 9	5.5 ±0.5	0 8 ±0 8
T_3	71 5 ±3.8	63.1 ±4.2	2.96 ±0.22	3.20 ±0.43	2.8 ±0 5	7.5 ±0.7	3.1 ±0.9

decrease in cardiac output proportional to the decrease in arterial pressure. In one-third of all patients 50 mm Hg was unobtainable, but the addition of SNP proved effective and was well tolerated by these particular patients.

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BLOOD CYANIDE AND THIOCYANATE CONCENTRATIONS PRODUCED BY LONG-TERM THERAPY WITH SODIUM NITROPRUSSIDE

C. J. VESEY AND P. V. COLE

SUMMARY

Blood cyanide (HCN) or plasma thiocyanate (SCN) concentrations, or both, were measured in 30 patients (ages 11 months–72 yr) receiving sodium nitroprusside (SNP) for 12–314 h. Sequential measurements in three of these patients (infused 5, 12 and 13 days) showed that HCN concentrations varied with dose rate, while SCN concentrations increased linearly with increasing SNP dose. The accumulated data confirmed that the rate of administration (0.3–6.5 $\mu g\ kg^{-1}\ min^{-1}$) determined the plasma HCN concentrations (0–3.8 $\mu mol\ litre^{-1}$; $y = 0.267x - 0.0733$; $r = 0.64$; $n = 51$; $P < 0.001$). Thus, if prolonged exposure to plasma HCN concentrations greater than 1 $\mu mol\ litre^{-1}$ is to be avoided, the maximum safe sustained dose rate *of SNP will lie near to 4 $\mu g\ kg^{-1}\ min^{-1}$. Likewise, the SCN results (30–880 $\mu mol\ litre^{-1}$) confirmed the close relationship between plasma concentrations and the total SNP dose (0.44–32.9 $mg\ kg^{-1}$; $y = 24.6x + 74.9$; $r = 0.95$, $n = 51$, $P < 0.001$). Therefore, we suggest that, to avoid SCN toxicity (plasma SCN > 1.75 $\mu mol\ litre^{-1}$), in the absence of SCN monitoring,* the total SNP dose *should be less than 70 $mg\ kg^{-1}$ in patients with normal renal function.*

Sodium nitroprusside (SNP) is used widely in the long-term management of a variety of cardiovascular emergencies (Zietsche and Franciosa, 1977; Cohn and Burke, 1979). Its evanescent action, attributable in part to rapid breakdown in the blood stream (Kreye, 1980), is a major advantage, allowing a fine control of its therapeutic action. As a result, however, there are two potential problems during long-term infusion. First, the patient is exposed, for a prolonged period, to increased, but non-lethal concentrations of cyanide (HCN). Second, thiocyanate (SCN), a product of HCN detoxication, accumulates in the extracellular fluid and can itself produce toxic effects in high concentration (Wald, Lindberg and Barker, 1939; Russell and Stahl, 1942).

During deliberate hypotension, blood HCN concentrations are the major concern. These have been shown to be related to the total dose of SNP and various figures for safe limits have been published (Davies et al., 1975; Editorial, 1975; Vesey, Cole and Simpson, 1976; Aitken et al., 1977; Michenfelder, 1977). However, different criteria will apply to the long-term administration of SNP, because of both the inevitably prolonged exposure to HCN, and the potential for SCN toxicity. To date, few dose limits have been recommended (Michenfelder and Tinker, 1977; Schulz, Dohring and Rathsack, 1978). We have measured plasma and RBC HCN or plasma SCN concentrations or both, in 30 patients who were receiving prolonged therapy with SNP for various cardiovascular problems, so as to make tentative suggestions for safe maxima for rate of administration and total dose of the drug.

PATIENTS AND METHODS

Blood samples were obtained during or near the end of infusion, or at both times, from a series of 30 patients (aged 11 months–72 yr) undergoing long-term therapy with SNP for periods of 12–314 h. The blood was taken into heparinized syringes and transported in ice and water to the laboratory for immediate separation, and determination of HCN concentration. Plasma for SCN measurement was stored at −20 °C and analysed later. In three of the patients, more detailed studies were undertaken by taking multiple samples. Cyanide data from six

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patients were rejected subsequently: four, because the dose rate either was not recorded at the time of sampling, or had been altered shortly before the blood was taken, and in the other two because hydroxycobalamin and isosorbide dinitrate had been administered, and it was considered that these could have altered HCN disposition in the blood. In addition, SCN values from two patients were rejected because of acute renal failure, and a third patient's plasma sample was lost.

As previously described (Vesey, Cole and Simpson, 1976; Vesey and Wilson, 1978), HCN was isolated from 5–10 ml of both plasma and saline-washed, packed red cells, by acidifying with three volumes of 10% trichloroacetic acid (TCA) and transferring the HCN into a small volume of sodium hydroxide 0.2 mol litre^{-1} by means of a stream of scrubbed nitrogen (Boxer and Rickards, 1951). SCN was determined in protein-free extracts of plasma (0.5 ml + 4.5 ml of 5% TCA in duplicate and centrifuged for 20 min at 2500 rev min^{-1}. Measurement of the isolated HCN and of the extracted SCN was made by means of an autoanalytical technique (Vesey and Kirk, 1985).

RESULTS

The results for the three individual patients studied in detail are shown in figures 1, 2 and 3. In the first patient both plasma HCN (ranging from 0.08 to 0.26 μmol litre^{-1}) and red cell HCN (2.10–6.14 μmol litre^{-1}) concentrations varied with the rate of infusion (0.49–1.99; mean SNP 0.94 μg kg^{-1} min^{-1}). Plasma HCN concentration showed a significant correlation with dose rate at the 5% level. In contrast, plasma SCN increased continuously from a value of 48 μmol litre^{-1}, at the beginning of infusion, to 500 μmol litre^{-1} after a total dose of SNP 1010 mg (17.7 mg kg^{-1}) had been infused over 13 days, and was significantly correlated with the cumulative

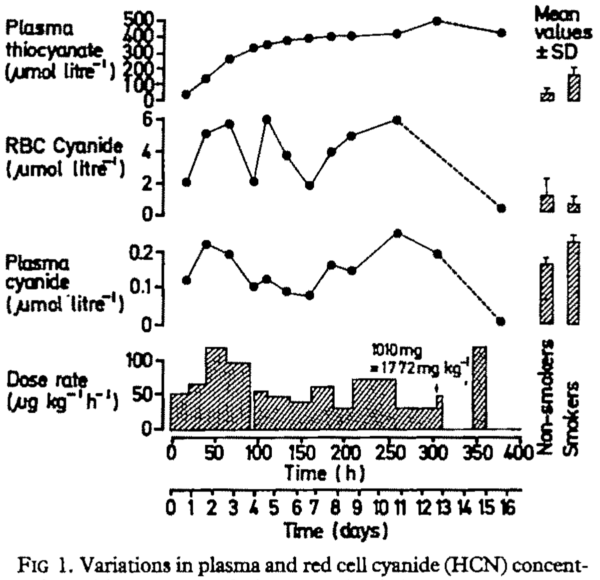

FIG 1. Variations in plasma and red cell cyanide (HCN) concentration with dose rate of nitroprusside (SNP), and increases in plasma thiocyanate (SCN) concentration with increasing SNP dose in a 50-year-old female patient with myocardial infarction and ischaemic VSD. To place these HCN and SCN values in perspective, mean values ± SD (Wilson and Matthews, 1966; Vesey and Wilson, 1978) for healthy smokers and non-smokers are shown on the right of the figure. (The apparent anomaly that smokers have a lower RBC HCN concentration than non-smokers may result from the fact that only a small sample of subjects have so far been studied (Vesey and Wilson, 1978) and that blood samples were not taken immediately after smoking, so that induced cyanide metabolism has produced lower values.) *Correlations:* Plasma HCN *v.* SNP dose rate: $r = 0.58$, $n = 11$, $P = 0.05$; $y = 0.0847x + 0.0739$. RBC HCN *v.* SNP dose rate: $r = 0.48$, $n = 10$, $P = 0.05$; $y = 1.72x + 2.73$. SCN *v.* total SNP dose: $r = 0.96$, $n = 11$, $P < 0.001$; $y = 23.7x + 81.2$.

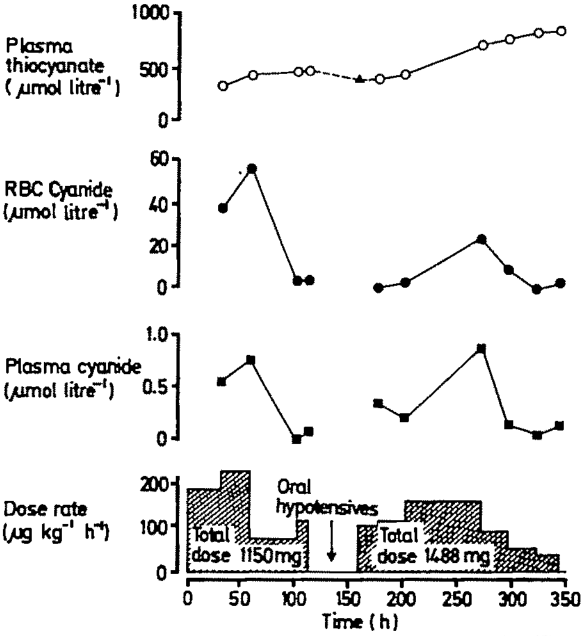

FIG 2. Changes in dose rate, RBC and plasma cyanide (HCN) concentrations, and plasma thiocyanate (SCN) concentration in a 51-year-old male patient with a dissecting aortic aneurysm. *Correlations:* Plasma HCN *v.* SNP dose rate: $r = 0.85$, $n = 10$, $P < 0.01$; $y = 0.266x - 0.188$. RBC HCN *v.* dose rate: $r = 0.92$, $n = 10$, $P < 0.01$; $y = 16.9x - 16.6$. Plasma SCN *v.* SNP dose: (a) first period of infusion $r = 0.97$, $n = 4$, $P < 0.05$; $y = 14.4x + 295$; (b) second period of infusion $r = 0.998$, $n = 6$, $P < 0.001$; $y = 25.4x + 384$. This patient was a smoker (20 cigarettes per day) and, therefore, would have started with an increased plasma SCN concentration (Vesey, 1981)—as shown by the regression equation. ▲ = Calculated SCN value.

dose of SNP (fig. 1). A further blood sample, taken 18 h after the end of the infusion, demonstrated the absence of HCN in the plasma. The red cell concentration (HCN 0.64 µmol litre^{-1}) had decreased to well within the normal range (Vesey and Wilson, 1978), and plasma SCN concentration had decreased to 416 µmol litre^{-1}.

A similar pattern was seen in the second patient (fig. 2), whose clinical management has been reported previously (Hillman and Krapez, 1978). Again, HCN concentrations varied with the rate of SNP infusion, but because of the higher dose rates (SNP 1.14–3.79, mean 2.31; and 0.62–2.61, mean 1.79 µg kg^{-1} min^{-1}, in the two periods of infusion) the maximum concentrations of HCN were higher than in the previous patient (0.76 and 0.88 µmol litre^{-1} in plasma; 57.3 and 22.9 µmol litre^{-1} in RBC). Plasma and red cell HCN concentrations correlated significantly with dose rate. Apart from the 48-h period when oral hypotensive agents were used, plasma SCN concentration increased uniformly with the increasing dose of SNP and correlated significantly with the dose of SNP. This patient was a smoker (20 cigarettes a day) and had, initially an increased plasma SCN concentration (Vesey, 1981). This increased to SCN 510 µmol litre^{-1} at the end of the first infusion (after a total of SNP 15.4 mg kg^{-1}) and, following the second infusion (SNP 19.98 mg kg^{-1}), increased to a final value of SCN 880 µmol litre^{-1}.

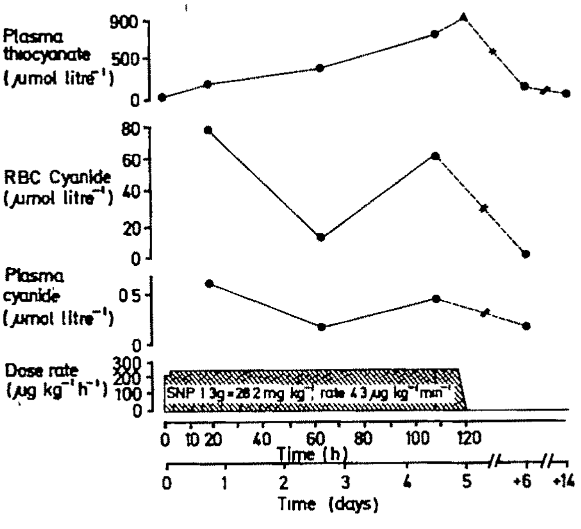

FIG 3. Plasma and red cell cyanide (HCN) and plasma thiocyanate (SCN) concentrations, and dose rate in a 51-year-old female patient treated for ergotamine poisoning. *Correlation:* Plasma SCN *v*. SNP dose. $r = 0.99$, $n = 4$, $P = 0.01$; $y = 26.6x + 65$. Also shown are HCN concentrations 6 days after the end of infusion and plasma SCN concentrations before the start of the infusion, and 6 and 14 days after the infusion ended. ▲ = Calculated plasma SCN value.

The third patient (fig. 3) received SNP 28.2 mg kg^{-1}. Plasma SCN concentration increased from a pre-infusion value of 79 µmol litre^{-1} to a final measured value of 850 µmol litre^{-1} towards the end of the infusion, and showed a significant correlation with the dose of SNP. Since both the rate of infusion and the increase in plasma SCN were uniform it can be calculated that the concentration had increased to about SCN 910 µmol litre^{-1} when the infusion was finally stopped at a total dose of SNP 30.5 mg kg^{-1}. Fourteen days later it had decreased to SCN 90 µmol litre^{-1} plasma. Although the infusion rate was maintained constant at SNP 4.3 µg kg^{-1} min^{-1}, RBC and plasma HCN concentrations in the second blood sample (12.5 and 0.21 µmol litre^{-1}, respectively) were considerably lower than in either the first or last samples taken during infusion (HCN 80.3 and 0.71, 62.7 and 0.56 µmol litre^{-1}, respectively). This could be a result of the fact that the second blood sample was taken during the administration of plasma protein fraction (PPF), a volume of PPF 250 ml having been infused up to this point. This is receiving further study.

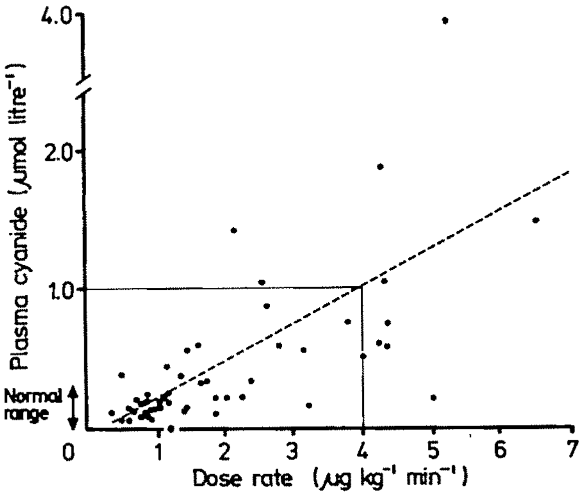

FIG 4. Plasma cyanide (HCN) concentrations obtained from 24 of the patients, plotted against the nitroprusside (SNP) infusion rates. *Correlation:* $r = 0.64$, $n = 51$, $P < 0.001$; $y = 0.267x - 0.0733$. The diagram also indicates that a critical value of HCN 1 µmol litre^{-1} in plasma corresponds to an infusion rate of SNP 4 µg kg^{-1} min^{-1}.

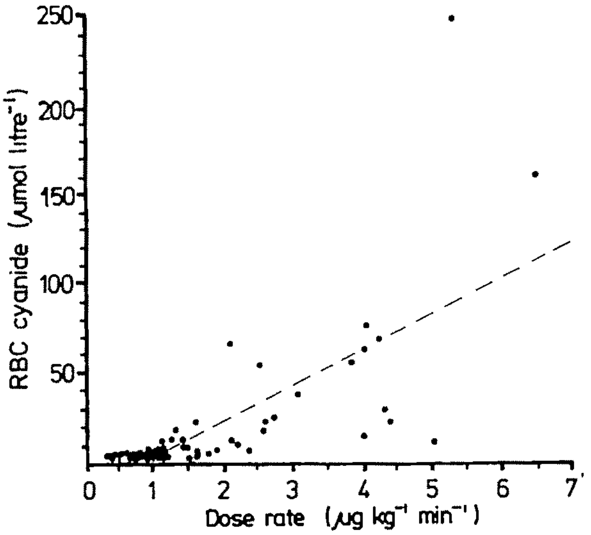

FIG 5. Red cell cyanide (HCN) concentrations recorded in the same patients as in figure 4, plotted against infusion rate of sodium nitroprusside (SNP). *Correlation:* $r = 0.71$, $n = 50$, $P < 0.001$; $y = 20.6x - 17.9$. Red cell HCN *v.* plasma HCN: $r = 0.92, n = 50, P < 0.001$.

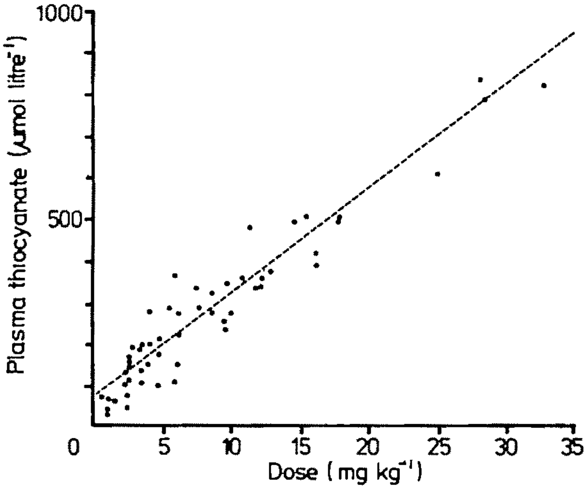

FIG 6. Plasma thiocyanate (SCN) concentrations, recorded in 27 patients, plotted against sodium nitroprusside (SNP) dose. *Correlation:* $r = 0.95$, $n = 51$, $P < 0.001, y = 24.6x + 74.9$. Assuming the linear relationship between plasma thiocyanate and nitroprusside dose holds at higher values, extrapolation suggests that a critical value of SCN 1725 μmol litre^{-1} in plasma corresponds to an infused dose of SNP 70 mg kg^{-1}.

Plasma and red cell HCN concentrations in relation to dose rate of SNP for 24 of the patients are shown in figures 4 and 5. Plasma SCN concentrations from 27 patients are related to the cumulative doses of SNP in figure 6. Plasma HCN concentrations (fig. 4) showed a significant correlation with the rates of infusion ($r = 0.64, n = 51, P < 0.001$). RBC concentrations of HCN (fig. 5) showed a similar correlation with dose rate ($r = 0.71$, $n = 50$, $P < 0.001$), and a close correlation with the plasma HCN concentrations ($r = 0.92$, $n = 50$, $P < 0.001$). The distribution of the few HCN concentrations at high infusion rates suggests that there could be an exponential relationship to dose rate, but logarithmic transformation did not improve the correlation for plasma HCN concentration ($r = 0.61$) although it did for RBC HCN concentration ($r = 0.82$). Neither RBC HCN or plasma HCN concentrations showed any relation to total dose of SNP; there was, however, a highly significant correlation between plasma SCN concentration and the total amount of SNP infused (fig. 6) ($r = 0.95$, $n = 51, P < 0.001$).

DISCUSSION

Blood cyanide concentration and dose rate of nitroprusside

Changes in HCN concentrations in two of the individual patients studied in detail (figs 1, 2) show an obvious relation to the variations in SNP infusion rates. This is confirmed by the significant correlations between both plasma and RBC HCN concentrations and SNP dose rate for all patients (figs 4 and 5). The results further show (figs 1 and 4) that plasma HCN concentration may increase above normal values when infusion rates are greater than SNP 1 μg kg^{-1} min^{-1}. Since the supply of thiosulphate is the limiting factor determining the rate of HCN detoxication (Sorbo, 1975), differences in HCN concentrations between patients with similar SNP dose rates may be the result of individual differences in this supply. Indeed, physiologically increased concentrations of thiosulphate lead to an increased rate of HCN detoxication (Tinker and Michenfelder, 1980; Braverman, Ivankovich and Shah, 1982). When SNP is infused rapidly, HCN may be liberated faster than it can be detoxicated by the tissues because of the limited availability of thiosulphate. As a result, blood concentrations of HCN will increase above normal, and will tend to lag behind any subsequent reduction in infusion rate. These two factors, individual differences in thiosulphate supply and the effect of prior infusion rates, may explain the wide scatter in plasma and RBC

HCN concentrations, and the relatively low correlations with recorded SNP infusion rates in this study.

In order to limit the increase in plasma HCN concentrations to less than 3 μmol litre^{-1} (that is, one-third of the calculated minimum lethal plasma concentration) a maximum dose of SNP 1.5 mg kg^{-1} was recommended for hypotensive anaesthesia (a dose rate of 8.3–25 μg kg^{-1} min^{-1}) for infusions of between 1 and 3 h (Vesey, Cole and Simpson, 1976). Whilst this has gained support from the findings of other workers (Michenfelder, 1977); some have suggested higher (SNP 3–3.5 mg kg^{-1} (Davies et al., 1975; Editorial, 1975)) and some lower (0.5 mg kg^{-1} (Aitken et al., 1977)) maximum doses. However, it is certain that a lower safe maximum dose rate is necessary for long-term infusions. Chronic exposure to HCN is likely to exhaust detoxication mechanisms, particularly in sick patients, and cyanide concentrations which may be tolerated in the short-term, may prove toxic over longer periods. In fact Lawrence (1947) showed that, in anaesthetized dogs, the longer the time of sodium cyanide infusion, the lower was the lethal dose rate.

There is very little published information to guide us in deciding what is a safe plasma HCN concentration when maintained for several days or weeks. For example, smokers continuously expose themselves to relatively large amounts of HCN, but their plasma concentrations are only slightly greater than those of non-smokers (Wilson and Matthews, 1966) (fig. 1). One cigarette yields up to 0.5 mg of HCN and 1.0 mg of nitriles (which release HCN *in vivo*) (Vesey, 1981). Thus, an inhaling smoker consuming 50 cigarettes a day would absorb at least HCN 25 mg. As a bolus, HCN 25 mg would be lethal. Over a 12-h period this would be equivalent to an average HCN intake of 34.7 μg min^{-1}, or 0.50 μg kg^{-1} min^{-1} in a 70-kg man. Since SNP contains 45% HCN by weight, this would be equal to an infusion of SNP about 1.0 μg kg^{-1} min^{-1} (also see Addendum). It would appear, therefore, that the body is able to tolerate this level of HCN exposure (except in some acquired or inherited toxic amblyopias (Wilson, 1965; Foulds, Bronte-Stewart and Chisholm, 1968)). Indeed, figure 4 shows that at infusion rates of SNP up to 1 μg kg^{-1} min^{-1} there was only one recorded plasma HCN concentration above the normal range (Wilson and Matthews, 1966).

In contrast to the near normal HCN concentrations in smokers, Osuntokun (1973) reported significantly increased mean plasma HCN concentrations of 1.1 μmol litre^{-1} in subjects ingesting HCN in their staple diet of cassava, and suffering from tropical ataxic neuropathy as a consequence. Both the neurological symptoms, and a form of diabetes which it is believed is caused by ingested HCN (McMillan and Geevarghese, 1979), develop over several years of exposure to HCN. Since this value of plasma HCN is associated with symptoms of chronic toxicity, it would be wise to try to limit plasma concentrations to HCN 1 μmol litre^{-1} or less during long-term infusions of SNP. The regression of plasma HCN upon dose rate in figure 4 suggests that, on average, an infusion of 4 μg kg^{-1} min^{-1} would result in a maximum of HCN 1 μmol litre^{-1}. Only one of the 42 measurements at infusion rates of SNP 4 μg kg^{-1} min^{-1} or below was significantly above HCN 1 μmol litre^{-1}. Although, above this infusion rate, three out of a total of eight plasma HCN measurements were well above this critical value, there are insufficient data to rule out a somewhat higher maximum for a safe dose rate. Indeed, Michenfelder and Tinker (1977) recommended a maximum dose rate of SNP 8 μg kg^{-1} min^{-1} for chronic infusion in man. However, this recommendation may be too high because it was based on 48-h infusions in dogs, which detoxicate HCN more rapidly than man (Vesey et al., 1979). Such a reservation is supported by the occurrence of lactic acidosis in two patients infused at SNP 8 μg kg^{-1} min^{-1} (Humphrey and Nash, 1978) and SNP 7 μg kg^{-1} min^{-1} (Mellino and Phillips, 1980), respectively, for 24 h. The maximum safe continuous dose rate which would avoid long-term toxic effects of HCN in adults may therefore lie at or above SNP 4 μg kg^{-1} min^{-1}, but certainly below SNP 8 μg kg^{-1} min^{-1}. The fetus and the neonate, however, are less able to detoxicate HCN (Fitzgerald, 1954) and the maximum rate for pregnant women and young children should be lower than this. Some support for this point is provided by the observations of Schulz and Roth (1982), who recorded toxic blood cyanide concentrations in a 10-day old child after a 24-h infusion at a rate of SNP 4 μg kg^{-1} min^{-1}, and by Goodlin (1983) who attributed the death of fetuses to HCN exposure during 36 h of SNP infusion in three pregnant women who did not themselves exhibit symptoms of toxicity.

Thiocyanate accumulation related to SNP dose

Since SCN is excreted by the kidneys at a relatively slow rate, because some 90% of that filtered by the glomeruli is reabsorbed (Pullman and McClure, 1954), plasma concentrations of the anion increase linearly throughout SNP administration, as illustrated by the measurements made in patients 1–3 (figs 1–3). Both in these three patients, and with the data obtained from the 27 patients, there was a close correlation between plasma SCN concentration and the cumulative dose of SNP. The slow rate of SCN excretion is further illustrated by the fact that the increase in plasma SCN concentration in patient 3 did not return to the pre-infusion value for 14 days. If there is a break in infusion, therefore, it cannot be assumed that plasma SCN will have decreased to a normal value. This was demonstrated in patient 2, in whom, after a gap of 48 h, the second period of infusion commenced with a calculated increase in plasma SCN concentration of 350 μmol $litre^{-1}$. Similarly, as this patient also demonstrates, smokers may already have a high plasma SCN concentration before infusion, and this should be taken into account.

Although SCN is generally considered to be non-toxic, it was shown early to have a weak hypotensive action (Pauli, 1903; Barker, 1936) and, until the late 1950s, patients with refractory hypertension were prescribed large doses of sodium or potassium thiocyanate to be taken by mouth over long periods, sometimes for many years. Toxic effects, such as anaemia, psychosis, coma and death, occurred at plasma SCN concentrations greater than 20 mg dl^{-1} or 3450 μmol $litre^{-1}$ (Garvin, 1939; Barker, Lindberg and Wald, 1941; Barnett, Jackson and Spaulding, 1951; Frohman and Klocke, 1963). Barker (1936), therefore, introduced the monitoring of plasma SCN concentrations during thiocyanate therapy and suggested that concentrations between 6 and 10 mg dl^{-1} (1035–1725 μmol $litre^{-1}$) decrease arterial pressure, while significant toxicity occurred only above 15–20 mg dl^{-1} (2590–3450 μmol $litre^{-1}$).

Although it has been shown that prolonged exposure to lower plasma concentrations affects thyroid activity (Folger and Rose, 1943; Rawson, Hertz and Means, 1943; Wood, 1975), a concentration of SCN 10 mg dl^{-1} (1725 μmol $litre^{-1}$ in plasma) is generally accepted as one that does not produce serious toxic effects (Tuzel, 1974; Palmer and Lasseter, 1975; Tinker and Michenfelder, 1976; Zietsche and Franciosa, 1977; Schulz, Dohring and Rathsack, 1978). Using the relationship between plasma SCN concentration and total dose of SNP established in this study (fig. 6), and assuming linearity at higher dose rates, a SCN concentration of 1725 μmol $litre^{-1}$ is likely to be attained in patients infused with a total dose of SNP 70 mg kg^{-1} over periods of up to 2 weeks (the maximum period covered by out study). At a dose rate of 4 μg kg^{-1} min^{-1} (or, for a 70-kg individual, approximately 400 mg day^{-1}), this SCN concentration would be attained in about 12 days. This compares with a maximum dose of SNP 250 mg day^{-1} (not expressed in terms of patient weight) for a period of 10 days, calculated by Schulz, Döhring and Rathsack (1978), for patients with renal impairment (SCN half-life of 7 days). These authors also show graphically the infusion times at which toxic concentrations of SCN would arise in such patients infused at rates of up to SNP 1000 mg day^{-1}. The much longer half-life of plasma SCN in patients with renal failure receiving SNP (9 days compared with 3 days in healthy subjects given SCN (Schulz, Bonn and Kindler, 1979)) makes monitoring of SCN concentrations mandatory in such patients. However, if these patients undergo dialysis then plasma SCN concentration will be decreased rapidly (Danzig and Kringe, 1955; Christensen and Williams, 1962).

In conclusion, therefore, it is suggested that the maximum safe sustained dose rate for long-term SNP infusions is less than 8 μg kg^{-1} min^{-1} (11.5 mg kg^{-1} day^{-1}), and near to 4 μg kg^{-1} min^{-1} (5.8 mg kg^{-1} day^{-1}). In addition we suggest that the maximum total dose of SNP is in the region of 70 mg kg^{-1} for periods of less than 14 days in patients with adequate renal function. In the presence of renal insufficiency the concentration of SCN should be monitored. The administration of hydroxycobalamin will aid in HCN detoxication and counteract any effect of SCN on haematopoiesis (Frohman and Klocke, 1963), but the continuous infusion of thiosulphate is not a suitable HCN antagonist during long-term SNP infusions, since it will increase the rate of SCN accumulation and produce hypovolaemia (Michenfelder and Tinker, 1977).

ADDENDUM

The calculation can be made in another way. The HCN concentration in cigarette smoke is variously quoted as 37.7–44.6 μg per 35-ml puff (Brunnemann, Yu and Hoffmann, 1977), 28–39 μg per 35-ml puff (Collins, Sarji and Williams, 1970), and 400 p.p.m. or 0.48 μg ml^{-1} (Darby and Wilson, 1967; Rickert, Robinson and Young, 1980). The total volume of smoke inhaled per cigarette is approximately 570 ml (Russell et al., 1982) and, therefore, for a smoker of 50 cigarettes per day (yielding say, HCN 0.88 μg ml^{-1}; that is, the mean of the highest and lowest yields of HCN quoted), the total HCN inhaled and—since HCN readily passes into the tissues—the amount absorbed = HCN 358 μg kg^{-1} in a 70-kg smoker. Over 12 h this would be equivalent to a dose of HCN 0.50 μg kg^{-1} min^{-1}. Since SNP releases 45.3% of its weight of HCN this average rate of intake in a smoker would be equivalent to an infusion of SNP 1.10 $\mu g\ kg^{-1}\ min^{-1}$.

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EFFECT OF INDUCTION OF ANAESTHESIA WITH ETOMIDATE ON CORTICOSTEROID SYNTHESIS IN MAN

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SUMMARY

The effects of a single bolus dose of etomidate 0.3 mg kg^{-1} or thiopentone 5 mg kg^{-1}, on the synthesis of corticosteroid hormones and adrenocorticotrophic hormone (ACTH), were compared for 24 h in 12 patients, undergoing minor surgery under general anaesthesia. Following opioid premedication i.m. and general anaesthesia, plasma cortisol concentrations decreased transiently within the first hour of anaesthesia in all 12 patients. The six patients who received etomidate had statistically higher plasma 11-deoxycorticosterone concentrations at 4 and 24 h than those who had received thiopentone ($P < 0.01$). Throughout the study, no difference in plasma cortisol, corticosterone or ACTH concentrations were found between the two groups. We have demonstrated a biochemical effect of a single bolus dose of etomidate consistent with incomplete inhibition of adrenocortical mitochondrial 11 β-hydroxylase activity, but no clinically significant adrenocortical suppression.

An increase in the mortality amongst trauma patients in an intensive care unit, coincident with the introduction of sedation using an infusion of etomidate, was reported by Ledingham and Watt (1983). Suppression of the adrenocortical secretion of cortisol was demonstrated when etomidate was infused to these patients (Finlay and McKee, 1982; Ledingham et al., 1983; McKee and Finlay, 1983).

The continued use of etomidate has been questioned (Committee on Safety of Medicines, 1983; Editorial, 1983), but in the absence of reported adverse effects from single bolus doses, its retention was advocated for the induction of anaesthesia in patients with asthma, drug allergy and peripheral circulatory failure (McDowall, 1983). In this study, the effects of a single bolus dose of etomidate or thiopentone on adrenocorticotrophic hormone (ACTH) production, and corticosteroid synthesis, were investigated in patients undergoing minor surgery under general anaesthesia.

PATIENTS AND METHODS

Twelve male patients, aged 23–78 yr (mean 49 yr, SD 17), without evidence of endocrine disease, and undergoing minor surgery, gave informed consent, and were included in the study. The surgical procedures included inguinal herniorrhaphy, ligation of varicose veins, haemorrhoidectomy and excision of sebaceous cysts. No patient was receiving regular medication, and all were premedicated with papaveretum 15 mg and atropine 0.6 mg i.m., approximately 1 h before surgery (mean 56 ± 16 min). They were allocated randomly to receive thiopentone 5 mg kg^{-1} or etomidate 0.3 mg kg^{-1} i.v. to induce anaesthesia, which was maintained with 1.5% halothane and 67% nitrous oxide in oxygen. Respiration was spontaneous. One patient in each group required tracheal intubation, which was facilitated with suxamethonium 1 mg kg^{-1}. Anaesthesia was induced between 10.45 a.m. and 4.15 p.m. and lasted 34 ± 16 min.

Blood samples were withdrawn 30 min before, immediately after, and at 15 min, 1, 4 and 24 h after the induction of anaesthesia. The plasma was separated, frozen and later analysed for plasma cortisol, corticosterone, 11-deoxycorticosterone, and ACTH concentrations.

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TABLE I. *Patient data (mean values ± SD). ns = not significant* ($P > 0.05$)

Induction agent	Age (yr)	Weight (kg)	Starting time			Duration (min)
Group 1:	50 ± 18	76 ± 6	10.45	14.20	15.10	32 ± 11
Thiopentone			14.00	15.00	15.15	
($n = 6$)						
Group 2:	48 ± 17	73 ± 10	11.40	13.00	14.55	35 ± 21
Etomidate			11.55	13.45	16.15	
($n = 6$)						
P	ns	ns		ns		ns

Plasma corticosterone and 11-deoxycorticosterone concentrations were measured by radioimmunoassay after extraction and partial purification by paper chromatography (Fraser et al., 1975). Plasma cortisol and ACTH concentrations were measured directly using kits supplied by Corning Ltd and CIS (UK) Ltd, respectively.

The coefficients of variation of the cortisol, corticosterone, 11-deoxycorticosterone and ACTH assays were 5.8%, 9.9%, 10.1% and 6.0%, respectively.

The results were analysed for statistical significance using the Mann-Whitney *U* test.

RESULTS

The two groups did not differ significantly with respect to age, weight, starting time and duration of anaesthesia (table I).

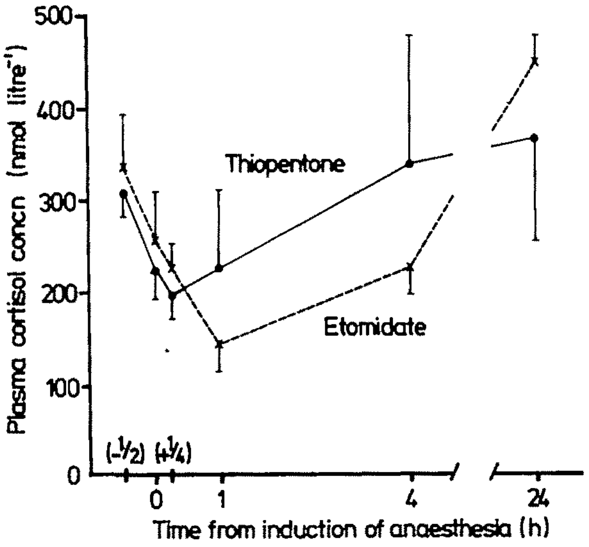

FIG. 1. Serial plasma cortisol concentrations (mean ± SEM). (All patients $n = 12$.)

TABLE II. *Serial plasma concentrations (mean ± SEM). Thiopentone:* n = *6; etomidate:* n = *6.* *$P < 0.01$

	Induction agent	Time from induction of anaesthesia					
		−30 min	0 min	15 min	1 h	4 h	24 h
Cortisol (nmol litre^{-1})	Thiopentone	307 ± 37	225 ± 40	105 ± 25	234 ± 72	344 ± 134	348 ± 98
	Etomidate	330 ± 67	257 ± 43	211 ± 23	151 ± 33	215 ± 40	445 ± 42
Corticosterone (nmol litre^{-1})	Thiopentone	4.9 ± 1.9	2.7 ± 0.9	2.0 ± 0.5	7.5 ± 3.3	18.3 ± 11.5	13.3 ± 9.0
	Etomidate	17.4 ± 3.4	3.0 ± 1.1	0.7 ± 0.2	1.7 ± 1.2	4.7 ± 2.3	3.7 ± 1.3
11-Deoxycorticosterone (pmol litre^{-1})	Thiopentone	280 ± 50	220 ± 30	190 ± 40	590 ± 270	540 ± 200*	190 ± 30*
	Etomidate	260 ± 30	250 ± 20	260 ± 40	1700 ± 850	21900 ± 9200	3100 ± 910
ACTH (pmol litre^{-1})	Thiopentone	12 ± 2.8	9.5 ± 1.6	19 ± 6.6	17 ± 50	35 ± 19	12 ± 3.4
	Etomidate	15 ± 2.9	14.0 ± 2.4	19 ± 5.1	15 ± 5.4	19 ± 6.8	18 ± 3.4

TABLE III. *Plasma cortisol concentrations (mean values ± SEM). (All patients: n = 12). *Difference from plasma concentration at t = −30 min; ns = not significant*

	Time from induction of anaesthesia					
	−30 min	0 min	15 min	1 h	4 h	24 h
Cortisol (nmol litre^{-1})	318 ± 37	241 ± 29	199 ± 16	192 ± 39	280 ± 71	392 ± 56
*P	—	ns	<0.01	<0.05	ns	ns

Cortisol concentrations

At no time did the concentrations differ significantly between the two groups (fig. 1, table II). Taking all 12 patients together, there were statistically significant decreases in the cortisol concentrations at 15 min ($P < 0.01$) and 60 min ($P < 0.05$) from induction of anaesthesia compared with the control concentration (table III). However, cortisol concentrations remained within the laboratory reference range (150–690 nmol litre^{-1}).

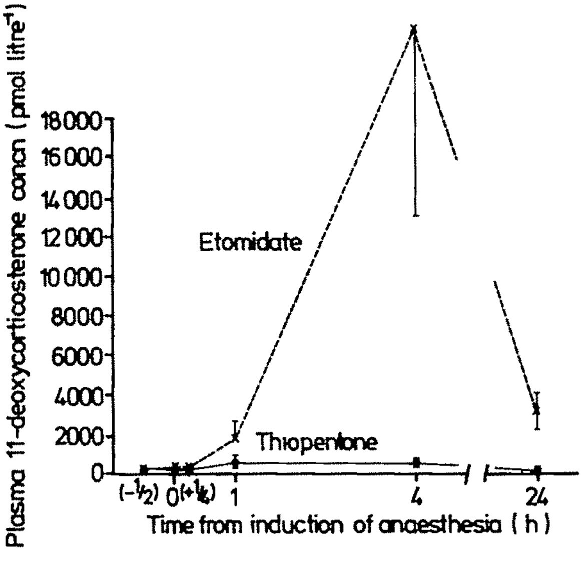

FIG 2. Serial plasma 11-deoxycorticosterone concentrations (mean ± SEM). (All patients n = 12.)

11-Deoxycorticosterone concentrations

At 4 and 24 h, plasma 11-deoxycorticosterone concentrations were significantly higher in the etomidate group than in the thiopentone group (fig. 2, table II). There was some increase in the etomidate group at 1 h, but the difference did not achieve statistical significance.

Corticosterone and ACTH concentrations

There was wide variation in all measurements and no trends or statistically significant differences were noted (table II).

DISCUSSION

Etomidate 0.3 mg kg^{-1}, when used to induce anaesthesia, produced a significant increase in 11-deoxycorticosterone concentrations at 4 and 24 h, when compared with thiopentone. No significant changes were seen in the plasma cortisol, ACTH or corticosterone concentrations.

Previously, attention has focused on the readily measured plasma cortisol concentration, and not on other adrenocortical precursors. The infusion of etomidate has been shown to suppress adrenocortical secretion of cortisol in man (Fellows, Byrne and Allison, 1983; Fellows et al., 1983; Sear et al., 1983), animals (Preziosi and Vacca, 1982; Fraser et al., 1984) and in adrenal cells *in vitro* (Kenyon et al., 1984). Such suppression may prejudice survival in the critically ill patient (Finlay and McKee, 1982; McKee and Finlay, 1983) in whom spontaneous adrenocortical failure is uncommon (Sainsbury, Stoddart and Watson, 1981).

Large doses of opioids can suppress the cortisol-stress response after surgery (Hall et al., 1978). The statistically significant (if small) decrease in plasma cortisol concentrations at 15 and 60 min in our patients is similar to that reported in three patients who had received opioid premedication (Sebel, Verghese and Makin, 1983). The transitory decreases in cortisol concentration are not known to be harmful and are likely to be at least partly a result of the use of opioid premedication and general anaesthesia, a common practice which occurred in 37% of patients who underwent surgery in our hospital between 1982 and 1984 (Miller, Sugden and Spence, 1983; Todd, Duthie and Spence, 1983).

Single bolus doses of etomidate 0.3 mg kg^{-1} have not been shown to suppress cortisol secretion abnormally. Fragen, Shanks and Molteni (1983) reported a decrease in cortisol concentration of undisclosed significance in women receiving etomidate, when compared with those who were given thiopentone. As in our study, Sebel, Verghese and Makin (1983) failed to show a difference in plasma cortisol concentrations between patients given either thiopentone or etomidate, and the mean plasma cortisol concentrations in all three studies remained within the physiological range.

The disproportionate increase in plasma 11-deoxycorticosterone concentrations is consistent with an inhibition of 11 β-hydroxylase activity and agrees with previous findings in dogs infused with etomidate (Fraser et al., 1984), and in bovine adrenocortical cells incubated with etomidate *in vitro* (Kenyon et al., 1984). That corticosterone and cortisol concentrations remained within the normal range suggests that the inhibition was incomplete and compensated by an increase in ACTH secretion. However, because of the marked variability in the ACTH concentrations measured, this increase could not be demonstrated statistically. In previous studies, evidence was obtained of additional effects earlier in the biosynthetic pathway, and an interference with mitochondrial corticosteroid mixed function oxidase reactions, possibly by interaction with cytochrome P450, was postulated. Such an effect would not have been apparent from the assays performed here and, if present, may have been less marked because high etomidate concentrations were maintained for a shorter time

In summary, we have demonstrated a biochemical effect of a single bolus dose of etomidate 0.3 mg kg^{-1} on adrenocortical steroid synthesis. The accumulation of 11-deoxycorticosterone at 4 and 24 h is consistent with the known inhibition of 11 β-hydroxylase by etomidate (Owen and Spence, 1984). This inhibition was partial, as it failed to reduce the plasma concentrations of the hormones, cortisol and corticosterone, and there was no discernible increase in ACTH concentration. Thus, a bolus dose of etomidate 0.3 mg kg^{-1} causes no significant adrenocortical suppression.

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USE OF ATRACURIUM AND VECURONIUM IN PATIENTS WITH OESOPHAGEAL VARICES

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The response of patients with hepatic dysfunction, to the administration of non-depolarizing neuromuscular blocking drugs is frequently abnormal. Dundee and Gray (1953) showed that such patients could be resistant to tubocurarine, and resistance to pancuronium was described by Nana, Cardan and Leitersdorfer (1972) and Ward, Adu-Gyamfi and Strunin (1975). Not only may large doses of the drugs be required to produce muscular relaxation but, in addition, reversal of neuromuscular blockade with anticholinesterases may be inadequate (Strunin, 1977).

This paper describes the clinical use of two non-depolarizing myoneural blockers, atracurium and vecuronium, in patients with oesophageal varices associated with some degree of hepatic dysfunction. A comparison is made between the results obtained in such patients and those from normal patients in which identical techniques of anaesthesia and monitoring were used (Hunter, Jones and Utting, 1982a, b, 1984).

This investigation is not intended to give a definitive solution to the problems involved in using these agents in patients with severe or terminal hepatic failure. Patients with oesophageal varices and less severe hepatic dysfunction are found much more commonly in surgical practice. The operations in this series were relatively short. Nevertheless, with the introduction of sclerotherapy, prolonged operations on patients with liver dysfunction have become uncommon.

SUMMARY

The effects of atracurium (initial dose 0.5 mg kg^{-1}; incremental doses 0.2 mg kg^{-1}) and vecuronium (initial dose 0.1 mg kg^{-1}; incremental doses 0.04 mg kg^{-1}) are described in patients with portal hypertension and some degree of liver dysfunction, and the findings compared with those from normal patients. With these doses there was no evidence of gross resistance to the two neuromuscular blockers in the patients with liver problems, although the duration of action of the initial dose was somewhat shorter, and the same may have been true of incremental doses. The method of elimination would suggest that atracurium may be the better drug in patients with severe liver dysfunction, but the use of small doses of vecuronium is not contraindicated in this type of patient.

PATIENTS AND METHODS

Patients

The patients studied were scheduled for injection sclerotherapy to oesophageal varices secondary to liver disease (table I). Some patients were treated as emergencies after acute episodes of bleeding, whilst others were undergoing a course of elective sclerotherapy. Patients in whom there was a considerable risk of inhalation of gastric contents at the induction of anaesthesia (for example, on account of active bleeding) were excluded from the study because it was felt that a rapid sequence induction using suxamethonium would be appropriate in these particular patients.

Thirty patients (21 male) with oesophageal varices were studied; 22 received atracurium and 20 vecuronium. Twelve patients received both agents, the

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TABLE I. *Causes of portal hypertension in the patients in the sclerotherapy group*

Diagnosis	Number
Alcoholic cirrhosis	11
Portal vein thrombosis	4
Neonatal sepsis (1)	
Polycythaemia rubra vera (1)	
Paroxysmal nocturnal haemoglobinuria (1)	
Unknown aetiology (1)	
Micronodular cirrhosis (unknown aetiology)	3
Macronodular cirrhosis (unknown aetiology)	3
Chronic active hepatitis	3
Primary biliary cirrhosis	3
Cryptogenic cirrhosis (coeliac disease)	3
Chemical exposure (?)	1
Following partial hepatectomy (trauma)	1

interval between the two consecutive anaesthetics ranging from 3 days to 5 months.

Control patients (ASA grade I and II) were undergoing a wide variety of general surgical and gynaecological procedures; 25 received atracurium and 21 vecuronium. Further details have been given previously (Hunter, Jones and Utting, 1982a, b, 1984).

Details of sex distribution, age and weight of all the patients are presented in table II. Biochemical details of the patients with abnormal liver function are shown in table III and their hepatic function classified (Child, 1964) in table IV.

TABLE II. *Details of patients studied*

	Atracurium		Vecuronium	
	Normal	Liver problems	Normal	Liver problems
No.	25	22	21	20
Male	18	14	5	12
Female	7	8	16	8
Age (yr)				
Mean	48	50.5	50	56.1
Range	(21–77)	(14–79)	(23–81)	(30–83)
Weight (kg)				
Mean	61	63.0	63	63.1
Range	(42–76)	(37–81)	(45–86)	(40–82.5)

TABLE III. *Results of preoperative liver function tests in patients with liver problems: normal values are given in parentheses. Mean values (SD) are given. Figures for plasma ammonia concentration are from 16 patients in the atracurium and 17 in the vecuronium group only*

	Atracurium	Vecuronium
Total protein (g litre^{-1}) (57–76)	72.9 (8.2)	67.9 (8.6)
Albumin (g litre^{-1}) (30–50)	38.1 (6.3)	34.0 (5.4)
Globulin (g litre^{-1}) (23–35)	34.8 (7.0)	34.0 (6.8)
Ammonia (μmol litre^{-1}) (10–47)	56.7 (36.3)	56.7 (25.7)
Prothrombin ratio (1)	1.36 (0.36)	1.4 (0.3)
Kaolin cephalin clotting time (s)(42–44)	54.14 (8.8)	56.27 (7.6)
Alanine amino transferase (u. litre^{-1})(7–45)	42.14 (28.1)	60.3 (43.9)
γ-Glutamyl transferase (u. litre^{-1})(0–65)	142.7 (163.1)	257.7 (381.9)
Alkaline phosphatase (u. litre^{-1})(35–130)	228.3 (172.9)	275.9 (200.6)
Total bilirubin (μmol litre^{-1}) (12–17)	27.4 (24.2)	56.95 (72.04)

TABLE IV. *Classification of severity of liver disease in terms of hepatic functional reserve (Child, 1964) and numbers in each group*

	A Minimal	B Moderate	C Severe
Serum bilirubin (μmol litre^{-1})	< 34	34–50	> 50
Serum albumin (g litre^{-1})	> 35	30–35	< 30
Ascites	None	Easily controlled	Poorly controlled
Neurological disorder	None	Minimal	Advanced
Nutrition	Excellent	Good	Poor
No. of patients			
Atracurium	16	3	3
Vecuronium	8	9	3

Anaesthesia

Patients were premedicated with diazepam 10 mg by mouth 1 h before operation, but no premedication was given to patients with clinical signs of encephalopathy. Anaesthesia was induced with fentanyl up to 200 μg, droperidol up to 10 mg and thiopentone 75–750 mg. While the equipment for monitoring neuromuscular function was being attached to the patient, anaesthesia was maintained with nitrous oxide 5 litre in oxygen 2 litre, using a mask (with or without an airway) and a Magill attachment. Increments of fentanyl and thiopentone were administered, if required.

Following baseline measurements of neuromuscular function, the initial dose of the myoneural blocker to be studied was administered via a rapidly running infusion of 5% dextrose. The initial dose of atracurium was 0.5 mg kg^{-1}, and of vecuronium, 0.1 mg kg^{-1}. Controlled ventilation via the anaesthetic mask was established as soon as practicable and tracheal intubation attempted 90 s after the neuromuscular blocker had been administered. No topical analgesia was applied to the larynx.

The anaesthetist performing tracheal intubation assessed conditions as follows: conditions were classified as "good" if the vocal cords were abducted and there was no reaction to the passage of the tube; "adequate" if the only reaction was a slight cough; and "poor" if there was considerable coughing or other movement as the tube was passed.

Controlled ventilation was continued using 70% nitrous oxide in oxygen: the patient was taken into the operating theatre and surgery commenced. A circle system was used without an absorber, the fresh gas flow and tidal volume being adjusted to give an arterial carbon dioxide tension of about 5.3 kPa (Snowdon et al., 1975); an infra-red carbon dioxide analyser (Datex normocap), calibrated with a mass spectrometer, was used to determine end-tidal carbon dioxide tension.

Increments of fentanyl 25 μg were given if the arterial pressure or heart rate increased during the procedure. Increments of the neuromuscular blocking drug were given when the initial twitch response of the train-of-four had returned to 20% of its initial value. The incremental dose of atracurium was 0.2 mg kg^{-1}, and of vecuronium, 0.04 mg kg^{-1}.

At the end of the surgical procedure atropine 0.6 mg was administered followed by neostigmine 2.5 mg, 1 min later. If the height of the first twitch response of the train-of-four had not returned to 75% of control 4 min after the neostigmine had been given, atropine 0.6 mg was administered again, followed by neostigmine 2.5 mg after a further 1 min. Thus, in the patients who received two doses of neostigmine, the time interval between the two doses was 5 min.

When the first mechanical response to the train-of-four stimuli had returned to at least 75% of control (A′/A) and spontaneous ventilation was adequate, anaesthesia was discontinued and monitoring of neuromuscular function disconnected before the patient became conscious.

Once the patient was able to obey commands, he was asked to lift his head and to cough as a clinical assessment of muscle power. The patient was returned to the recovery ward where he was observed for approximately 1 h. Oxygen 35% was administered by mask to the patients with liver problems. The patient was interviewed in the ward the next day and questioned about subjective experiences. Specific questions were asked with regard to residual muscle weakness or diplopia.

Monitoring

Cardiovascular function. Heart rate and systolic arterial pressure (by palpation) were recorded at 1-min intervals during induction until the mechanical response to train-of-four stimulation had disappeared. During the rest of the anaesthetic, heart rate and arterial pressure were recorded at least every 5 min. The electrocardiogram was monitored continuously.

Blood-gas tensions. Blood-gas tensions were measured using a calibrated blood-gas analyser (Radiometer ABL2C) to supplement the data from the end-tidal sampler, and confirm that acid–base status was within physiological limits.

Neuromuscular function. The train-of-four stimulus (Grass S48) was used to assess neuromuscular function (Ali, Utting and Gray, 1971a, b; Ali and Savarese, 1976). Supramaximal stimuli were applied to the ulnar nerve at the wrist via adhesive skin electrodes at a frequency of 2 Hz for 2 s. The duration of each stimulus was 0.2 s and the interval between each train was 10 s. The force of thumb adduction was measured using a force-displacement transducer (Grass FT 03C). For convenience, the initial twitch heights were designated A, B, C and D, and, during blockade, A′, B′, C′ and D′. The following times were recorded: the time from administration of the initial dose of blocking drug until the first appearance of blockade; the time when the mechanical response completely disappeared or was maximally diminished; the time at which the response reappeared (when complete ablation had taken place), and the time until recovery of the first twitch height to 10% and 20% of the control height of the initial twitch. The effect of incremental doses

TABLE V. *Mean times (SD) to first depression of twitch response and to maximum depression or ablation (SD). The number of patients on which the data are based is indicated in each case. Statistical significance compared with the normal group of patients receiving atracurium:* *$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; *statistical significance with regard to normal patients receiving vecuronium:* †† $P < 0.01$

	Atracurium		Vecuronium	
	Normal	Liver problems	Normal	Liver problems
Time to first depression (s)	32 (13.6) $n = 25$	47.9*** (11.1) $n = 22$	49* (12.9) $n = 21$	68.8†† (25.3) $n = 20$
Maximum depression or disappearance (s)	109.7 (27.8) $n = 25$	186.3*** (89.7) $n = 22$	172.7** (156) $n = 21$	248.7 (138.7) $n = 20$

and the recovery of the response after the administration of neostigmine and atropine were monitored.

RESULTS

Initial dose: degree of neuromuscular blockade

In the patients with varices, the mechanical response to train-of-four stimuli was ablated completely in all but one of the patients who received atracurium (95.5%) and in this one patient A′/A was reduced to 2%, B′, C′ and D′ having disappeared. Of the 20 patients with varices given vecuronium, the mechanical response was completely ablated in 17 (85%): in one of the remaining three patients, A′ was reduced to 3% and B′, C′ and D′ disappeared completely; in the other two, however, A′ persisted at 13% and 17%, respectively, and B′, C′ and D′ were not ablated completely. All the 25 normal patients who received atracurium showed complete ablation of all twitch responses; for vecuronium the figure was 19 out of 21 (90%).

Initial dose: speed of onset of neuromuscular blockade

The times to the first depression of the train-of-four (table V) were longer with both drugs in patients with liver problems than in the normal patients. In addition, the times to maximal depression or disappearance of the response to the train-of-four were longer with both drugs in liver patients, although this was statistically significant only in the group receiving atracurium. The time to first depression was significantly longer with vecuronium than with atracurium in the control patients.

Conditions for endotracheal intubation

Conditions on tracheal intubation 90 s after the initial dose of relaxant are shown in table VI. The conditions provided by both drugs were not as good in the patients with liver problems as in the normal patients. In the doses used, conditions provided by atracurium appeared to be somewhat better than those provided by vecuronium.

Initial dose: duration of action

Details of recovery time from the initial dose of neuromuscular blocker are given in table VII. This shows the times to reappearance of the twitch response after the initial dose of drug (in those cases in which the twitch responses completely disappeared) for both drugs and for both groups of patients. Corresponding data are given for time to 10% and 20% recovery of the initial twitch height.

In patients with liver problems, both the time to 10% recovery and the time to the first increment (20%) appeared to be slightly shorter than in the control group given the same drug, although statisti-

TABLE VI. *Conditions for tracheal intubation 90s after initial dose Conditions were "good" if the cords were abducted and there was no response when the tube was passed; "adequate" if there was only a slight cough and "poor" if there was considerable coughing*

Conditions for intubation	Atracurium		Vecuronium	
	Normal	Liver problems	Normal	Liver problems
Good	15	3	8	1
Adequate	9	15	10	10
Poor	1	4	3	8

TABLE VII. *Mean times (SD) from initial dose of drug to reappearance of response (when there was complete ablation in the first place) and to 10% and 20% recovery. The number of patients on which the data are based is indicated in each case. Statistically significant difference when compared with normal atracurium:* *P <0.05, **P <0.01; *significant difference from normal vecuronium:* †P <0.05

	Atracurium		Vecuronium	
	Normal	Liver problems	Normal	Liver problems
Reappearance of response (min)	35 (7.6) n=24	23.4 (ns) (5.9) n=17	23* (5.0) n=17	18.3† (6.0) n=16
Time to 10% recovery of A'/A (min)	39 (9.7) n=25	29 (ns) (4.4) n=13	27* (8.0) n=19	23.2 (ns) (5.2) n=13
Time to 20% recovery of A'/A (min)	43.1 (11) n=16	34.1* (4.7) n=10	33.5 (6.7) n=19	27.3† (6.9) n=11

cal significance was achieved only for the time to 20% recovery with both drugs.

Incremental doses

Few incremental doses were given and no firm conclusions can be made. Nevertheless, the mean time to each comparable increment was shorter in those with liver problems than in the normal patients (table VIII).

Reversal of neuromuscular blockade

The number of patients receiving two doses of neostigmine 2.5 mg was similar for both agents: for atracurium 56% for normal patients and 75% for those with varices, for vecuronium 58% and 68%, respectively. (The results depend on the ratio A'/A present before the first dose of neostigmine was given. Among the normal group no mechanical response at all was evident in 5% receiving atracurium and 14% receiving vecuronium; in those with liver problems the percentages were rather higher—32% for atracurium and 35% for vecuronium.)

Figures 1 and 2 indicate graphically that the rate of return of the mechanical response in those patients with varices who were given two doses of neostigmine was similar whichever of the two neuromuscular blockers was considered, and this applied to both the ratios A'/A and D'/A.

Clinically acceptable antagonism of residual neuromuscular blockade was obtained in all patients. No patient complained of either residual muscle weakness or diplopia in the period after operation.

TABLE VIII. *Incremental doses of atracurium and vecuronium administered to normal patients and those with liver problems. Times (SD) are from the time the initial dose was administered. Statistically significant difference with reference to normal patients receiving atracurium:* *P < 0.05; *statistically significant difference with reference to normal patients receiving vecuronium:* †P < 0.05

	Atracurium				Vecuronium			
Increment	Normal		Liver problems		Normal		Liver problems	
No.	No.	Time (min)	No.	Time (min)	No.	Time (min)	No.	Time (min)
1	16	43 (11.2)	10	34* (4.7)	19	33** (7)	11	27† (6.9)
2	10	71 (19.6)	2	52 (15.5)	14	58 (12)	3	43 (16.6)
3	7	89 (21)	1	59	8	84 (19)	2	47 (1.4)
4	3	99 (40.3)	1	75	3	115 (23)		
5	2	129 (72.4)	1	91	1	181		
6	1	217.5						

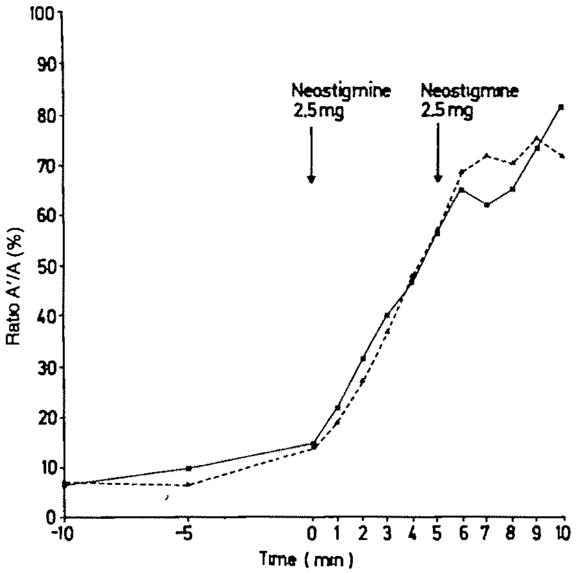

FIG 1 The effect of neostigmine on the mean of the ratio of A'/A in the groups of patients with liver dysfunction given atracurium (---) or vecuronium (——)

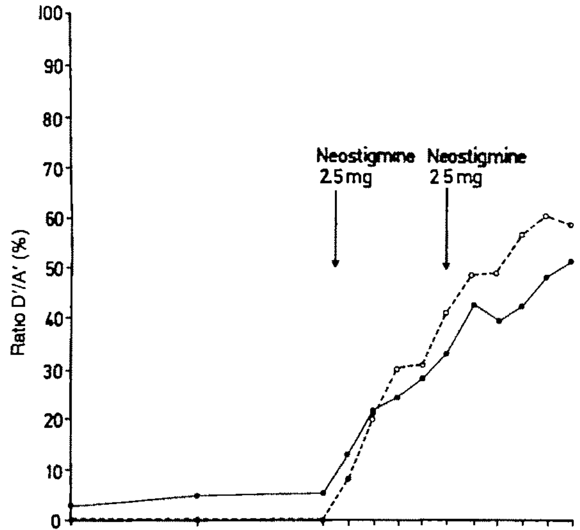

FIG. 2. The effect of neostigmine on the mean of the ratio D'/A' in the groups of patients with liver dysfunction given atracurium (---) or vecuronium (——)

Patients with more severe liver dysfunction

The results from the patients classified as Child's group C were analysed separately as representing the most severe degree of liver failure. Only six are available, three of whom received atracurium and three vecuronium. The values of all measured variables fell within the ranges obtained in the patients with less severe liver damage.

DISCUSSION

These two non-depolarizing neuromuscular blocking drugs appeared to be slower in onset of action in the patients with liver dysfunction than they were in the normal group. This finding is probably of no clinical importance since, in normal patients at least, suxamethonium is considerably faster than both and it seems likely that this will remain the relaxant of choice when a very rapid tracheal intubation is required as it would be, for example, in the presence of bleeding oesophageal varices.

A slower half-life of distribution in the patients with liver dysfunction might be the explanation of this slower speed of onset. The half-lives of distribution of pancuronium and fazadinium have been found to be considerably longer in cirrhotic than in normal patients (Duvaldestin et al., 1978; Duvaldestin et al., 1980), although it should be added that, in patients with cholestasis, no such prolongation was found with pancuronium or gallamine (Westra et al., 1981).

There was no evidence of gross resistance to either atracurium or vecuronium in the patients with liver disease. With atracurium there was some persistence of the first response of the train-of-four in one of patient with liver dysfunction, but the degree of persistence was small. Some persistence of the twitch is known to occur in normal patients with a dose of atracurium only a little less than that used (i.e. 0.4 mg kg^{-1}) (Foldes et al., 1983). With vecuronium, however, two patients with varices did show marked persistence of response to the train-of-four after the initial dose and this might be construed as some evidence of resistance. An interesting finding of this investigation was that the initial doses of both atracurium and vecuronium (and possibly the increments as well) lasted for a slightly shorter time in the patients with liver problems than they did in the normal controls (although the times taken for the initial twitch to recover from 10% to 20% of control height was similar with both drugs, and in both groups).

The liver does not seem to be involved to any great extent in the elimination of atracurium, which is mainly by the Hofmann reaction (Stenlake et al., 1983), and Ward and Neill (1983) found that the pharmacokinetics of atracurium did not differ much from normal in patients with both hepatic and renal failure. As far as vecuronium is concerned, this finding of a shorter duration of action in patients with liver problems appears to conflict directly with the results obtained by Duvaldestin and colleagues (1982). Using a bolus dose of vecuronium 0.2 mg kg^{-1}, these workers found that the time to 75% recovery of the single twitch height was nearly twice as long in cirrhotic as in normal patients (137 min compared with 75 min), and that the time between 25% and 75% recovery was tripled (68 min compared with 21 min). Pharmacokinetic data presented by these workers showed that, in the cirrhotic patients, the plasma clearance of vecuronium was only half that of normal controls; and it might be added that their pharmacokinetic data for controls agreed well with those of Cronnelly and co-workers (1983).

Preliminary work by the present investigators has confirmed that marked prolongation of action of vecuronium can indeed occur when large doses are given to patients with severe liver dysfunction. For example, in one such patient with obstructive disease given 0.2 mg kg^{-1}, recovery of the initial twitch height to 25% of control took 3 h, three times as long as in a group of normal controls.

There seems good evidence to suppose that the liver plays some part in the elimination of vecuronium, even though some spontaneous de-acetylation also occurs (Savage, Sleigh and Carlyle, 1980). It has been shown that exclusion of the hepatic circulation both intensifies the degree of blockade and increases its duration (Durant, Houwertjes and Agoston, 1979), and in rats biliary excretion accounts for about half of the administered dose of the blocking drug, urinary excretion being less important (Upton et al., 1982). It should be remembered that breakdown products of vecuronium may themselves have some degree of neuromuscular blocking activity (Marshall et al., 1982). In the human (although not, apparently, in the rat) the liver is involved in the removal of pancuronium, which is a close cogener of vecuronium (Agoston et al., 1973; Somogyi, Shanks and Triggs, 1977; Duvaldestin et al., 1978; Ward, Judge and Corall, 1982). In cirrhotic patients there is a marked slowing of the elimination of pancuronium (Duvaldestin et al., 1978) and fazadinium (Duvaldestin et al., 1980).

However, because a drug is, to some extent, eliminated by the liver does not mean that the termination of its action is, in all circumstances and with all doses, the result of hepatic excretion or metabolism. Matteo, Spector and Horowitz (1974) have emphasized that recovery from non-depolarizing neuromuscular blockade may depend on diffusion onto non-specific receptors (in cartilage, for example). It is possible that this sort of mechanism may be responsible for the termination of activity of the relatively small dose of vecuronium used in the current study, but when a dose twice as great is used, as by Duvaldestin and colleagues (1982), hepatic elimination becomes of importance.

An increased volume of distribution of both atracurium and vecuronium in the patients with liver problems might explain why the duration of action of both was somewhat shorter in these patients than in normal patients. Though Duvaldestin and colleagues (1982) failed to show this in the five cirrhotic patients to whom they administered vecuronium, an increase in the volume of distribution of pancuronium (Duvaldestin et al., 1978), fazadinium (Duvaldestin et al., 1980) and gallamine (Ramzan, Shanks and Triggs, 1981) has been found in cirrhotic patients. However, in some patients no such increase has been found (Somogyi, Shanks and Triggs, 1977; Duvaldestin et al., 1980; Westra et al., 1981).

A possible explanation of an increase in the volume of distribution is a decrease in binding of drugs to plasma protein, and Klotz (1976) has pointed out that diminished binding is not uncommon in liver disease; such an increase in the volume of distribution of drugs which are highly bound to plasma protein and extensively metabolized will diminish the effect on impaired elimination which is seen in liver disease. In the current study no correlation was found between plasma protein fractions and duration of action of the drugs, but this is far from conclusive. In the anaesthetic literature the suggestion has been made that it is an increased binding to plasma protein in liver disease which might be responsible for the apparent resistance to non-depolarizing agents in such patients (Aladjemoff, Dikstein and Shafrir, 1958; Baraka and Gabali, 1968). Ghoneim and co-workers (1973) investigated the plasma protein binding of tubocurarine in patients with hepatic disease and found it to be normal. Later, Duvaldestin and Henzel (1982), using both equilibrium dialysis and ultracentrifugation, could find no difference in the degree of binding in normal and cirrhotic patients in respect of tubocurarine, fazadinium, pancuronium and vecuronium.

The method of elimination of atracurium gives an *a priori* reason for considering it to be a better agent than vecuronium in patients with hepatic dysfunction, since the latter drug is eliminated, in part at least, by the liver. However, this investigation suggests that, in patients who have liver problems but who are not in the terminal stages of hepatic failure, the use of vecuronium 0.1 mg kg^{-1} is acceptable. As most patients presented for surgery have only mild or moderate dysfunction, the drug may be of use in those who are in this category but, in the present state of knowledge, caution is required if larger doses are used and careful monitoring would seem to be a wise precaution.

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COMPARISON OF THE COGNITIVE EFFECTS OF PREMEDICATION WITH HYOSCINE AND ATROPINE

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SUMMARY

An investigation was carried out comparing the nature and duration of the cognitive effects of atropine and hyoscine. Thirty patients undergoing a minor gynaecological operation were randomly assigned to one of three groups to receive hyoscine, atropine or placebo as premedication. A battery of psychological tests was administered before premedication, 30 min after premedication, and 1 and 3 h following operation. The tests included orientation questions, simple tasks such as reciting the alphabet, memory tests, a reaction-time test and two tests of visuo–motor co-ordination. The results showed that hyoscine had detrimental effects on memory and on motor tasks compared with placebo, while atropine did not. In addition, the effects on motor performance had not disappeared 3 h after operation.

The anticholinergic drugs, atropine and hyoscine are used widely as premedicants before general anaesthesia. A recent postal survey noted that, of anaesthetists in the United Kingdom and Ireland who replied, over 62% used anticholinergic drugs routinely for premedication, and that atropine and hyoscine were the most commonly used drugs (Mirakhur et al., 1978). The administration of these drugs before operation grew from the recognition of their antisialagogue and antivagal actions which counteracted the effects of the early anaesthetic agents (Shearer, 1960). However, increasing controversy over their effectiveness as premedicants has raised questions about the justification for their continued routine use before operation (Kessell, 1974; Leighton and Sanders, 1976; Mirakhur, Dundee and Connolly, 1979) particularly since the drugs can cause unpleasant side-effects, including restlessness, dizziness and blurring of vision, tachycardia, pain at the injection site and dryness of the mouth.

Since hyoscine has been reported to produce amnesia, there have been some studies of its effects in volunteers. These have reported significant effects of the drug on the ability to store new information (Safer and Allen, 1971; Drachman and Leavitt, 1974; Ghoneim and Mewaldt, 1975), but no effect on the ability to recall information which had been presented before its administration (Petersen, 1977). A few clinical studies have used simple tests of memory, such as asking patients whether they remembered the journey to the operating theatre (Pandit and Dundee, 1970), but these revealed only gross memory impairments. The effects of atropine on memory have not been investigated and only one study (Hardy and Wakely, 1962) has compared the effects of atropine and hyoscine. Few studies have attempted to look at the duration of any effect. Furthermore, comparisons between studies are difficult because of the different drug dosages and routes of administration used, as well as the variety of memory tests.

Any potential advantages gained by the use of atropine and hyoscine as premedicants must be weighed against their physiological as well as their cognitive side-effects. A comparison of the latter is important so that clinicians can be aware of their differential effects on memory and motor skills. As these drugs are used commonly as premedication in day case surgery, an investigation of the comparative *duration* of any cognitive side-effects may be useful in helping clinicians decide whether a patient is fit for discharge, especially when it is known that patients do not always heed the advice given about driving home. There is a clear lack of a comparative

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study of the nature and duration of the cognitive effects of atropine and hyoscine as they are used in clinical practice, and this study was designed to fill such a gap.

PATIENTS AND METHODS

Thirty patients (age range 22–55 yr) undergoing dilatation and curettage of the uterus were studied after giving informed consent. The patients performed a battery of psychological tests 30 min before premedication. They were then allocated randomly to one of three experimental groups: hyoscine 0.4 mg i.m., atropine 0.6 mg i.m. or placebo (physiological saline 1 ml) i.m. Testing was repeated 30 min after premedication. One hour after premedication, anaesthesia was induced with thiopentone 500 mg and maintained with 70% nitrous oxide and halothane in oxygen. The battery of tests was repeated 1 and 3 h after return to the ward. At all times, the test administrator and the patient were unaware of the identity of the premedicant drug.

Every patient performed the psychological tests in the following order:

(1) *Vocabulary* (from the Wechsler Adult Intelligence Scale). This gave an estimate of IQ and was administered on the first testing occasion only.

(2) *Mood Scales*. Patients were asked to rate how they felt, by placing a mark on each of six appropriately labelled 10-cm lines (Bored—Interested; Drowsy—Alert; Dizzy—Steady; Tense—Relaxed; Depressed—Elated; Anxious—Composed).

(3) *Orientation*. A series of six questions e.g. "What is today's date?"

(4) *Automatized Series*. Patients were asked to say the alphabet, months of the year and days of the week (time scored).

(5) *Alphabet Task*. Patients were asked to imagine the letters of the alphabet one by one and to say all those rhyming with the word "tree" (time and omissions scored).

(6) *Digit Span*. Forwards and backwards as in the WAIS, with four different versions for each testing occasion (forwards and backwards scores obtained).

(7) *Choice Reaction Time Task* (CRT). Patients were tested using the Leeds Psychomotor Tester. In this task 6 LED were arranged in a semi-circle on a board with a button adjacent to each. Patients placed an index finger on a central button and when one of the LED lit up, they had to press the button adjacent to it as quickly as possible, thus extinguishing the light. The test box automatically recorded response latencies (time to lift finger off the central button) and total reaction times (time to extinguish the light). Fifteen CRT were collected on each testing occasion, and patients were allowed practice trials on the first occasion only.

(8) *Memory Test*. Four lists, of 12 words each, were compiled for the four testing occasions. The words were read out at the rate of one per second and patients were asked to recall each list immediately following presentation (immediate recall) and again at the following testing occasion (delayed recall). The words were equated for familiarity according to Thorndike and Lorge (1944).

(9) *Cancellation Task*. Patients were instructed to cross out, as quickly as possible, all letters *P* in six rows of 25 random typed capital letters, on the first testing occasion and three other versions requiring them to cross out the letters *R*, *A* and *B* were compiled for the further testing occasions (time and errors scored).

(10) *Gibson Spiral Maze Test* (Gibson, 1978). Patients were instructed to draw a continuous line through the maze as quickly as possible without touching the edges or the circles within it (time and errors scored).

RESULTS

There were no significant differences between the ages of the patients in the three experimental groups. Patients were tested at the times set out in the method; however, carrying out this study in the setting of a busy hospital ward where the time that patients went into the operating theatre varied from day to day, meant that the intervals between test times were not constant. These intervals were compared, and found to be not significantly different between the three groups.

One-way analyses of variance were carried out to compare the three treatment groups on each test score for the four different testing occasions (trials 1, 2, 3 and 4). In addition, difference scores between trials 1 and 2, 2 and 3, 3 and 4, and 1 and 4 were computed for each test and further one-way analyses of variance carried out to compare the treatment groups, this being a more powerful analysis of the results.

In all, 159 of these analyses were performed and there were 25 significant results ($P < 0.05$). Eight such results would be expected by chance. This, as well as consistency among those test scores producing significant results, makes it unlikely that all of these results were attributable to chance. Table I details the tests and the trials on which the treatment groups were found to perform significantly differently, and also shows which of the three groups performed significantly differently from each other (Tukey's Honestly Significant Difference test (Tukey, 1949)).

TABLE I. *Significant differences shown between treatment groups (H = Hyoscine, P = Placebo, A = Atropine) on the different testing occasions (T1 = before premedication, T2 = 30 min after premedication, T3 = 1 h after operation, T4 = 3 h after operation*

Test	Trial	Treatment groups performing significantly differently		
Digit Span	T2	H *v*. P	A *v*. P	$P<0.05$
(Backwards)	T3	H *v*. P		$P<0.01$
Mood Scale	T3–T2	H *v*. P		$P<0.05$
(Bored—Interested)	T4–T3	H *v*. P		$P<0.05$
Mood Scale (Anxious—Composed)	T3–T2	H *v*. P		$P<0.05$
Orientation	T4	H *v*. P	H *v*. A	$P<0.01$
	T4–T1	H *v*. P	H *v*. A	$P<0.01$
Memory	T1	H *v*. P		$P<0.05$
(Immediate)	T2	H *v*. P	H *v*. A	$P<0.01$
	T3	H *v*. P	H *v*. A	$P<0.001$
	T4	H *v*. P	H *v*. A	$P<0.05$
Memory	T3	H *v*. P		$P<0.05$
(Delayed)	T4	H *v*. P	H *v*. A	$P<0.01$
Choice RT	T4	H *v*. P	H *v*. A	$P<0.01$
(Total)	T4–T1	H *v*. P	H *v*. A	$P<0.05$
Choice RT	T4	H *v*. P		$P<0.01$
(Latency)	T4–T1	H *v*. P	H *v*. A	$P<0.01$
Cancellation	T3	H *v*. P	H *v*. A	$P<0.01$
(Time)	T4	H *v*. P		$P<0.05$
	T3–T2		H *v*. A	$P<0.05$
	T4–T1	H *v*. P	H *v*. A	$P<0.01$
Cancellation (Errors)	T3	H *v*. P	H *v*. A	$P<0.01$
Gibson Maze	T3	H *v*. P		$P<0.05$
(Time)	T4		H *v*. A	$P<0.05$
	T4–T1		H *v*. A	$P<0.05$

Test results

The patients allocated to the three treatment groups did not differ significantly from each other on the Vocabulary test. The treatment groups did not differ significantly on any comparison on the automatized series, on the alphabet task, or on the forwards digit span task. On the backwards digit span test, patients given hyoscine and patients given atropine performed significantly worse than the placebo group in trial 2 (after drug administration) ($P < 0.05$). In trial 3, the hyoscine group continued to perform significantly less well than the placebo group ($P < 0.01$), but all differences between the groups had disappeared by trial 4 (3 h after return from the operating theatre).

On all of the rest of the tests, the significant differences were either between the hyoscine group and the placebo group or between the hyoscine group and both the placebo and the atropine groups, while there were no significant differences at any time between the atropine and the placebo groups.

Mood scales. Patients given hyoscine rated themselves as being significantly less bored than patients given the placebo, in trial 3, 1 h after return from the operating theatre, compared with trial 2, 30 min after drug administration ($P < 0.05$), and in trial 4 (3 h after return from the operating theatre) compared with trial 3 ($P < 0.05$). They also rated themselves as being significantly less anxious than patients in the placebo group in trial 3 compared with trial 2 ($P < 0.05$).

Orientation. Patients given hyoscine scored significantly fewer points on the orientation questions than both the placebo and the atropine groups, in trial 4, and in trial 4 compared with trial 1 ($P < 0.01$ in both cases). This was the result of their inability to answer one question correctly ("What is the time?") while patients in the other two groups were always able to estimate the time correctly to the nearest half-hour.

Memory tests. Patients who received hyoscine recalled significantly fewer words than patients given atropine and those given the placebo in trials 2 ($P < 0.01$), 3 ($P < 0.001$) and 4 ($P < 0.05$). However, they had recalled significantly fewer words than the placebo group only, in trial 1 (before drug administration) ($P < 0.05$). The comparisons of the difference scores between trials were not significant, despite an increase in the levels of significance of the effects found between the hyoscine and the other two groups in trials 2 and 3, which indicated that patients who had received hyoscine recalled fewer words immediately compared with patients who had received atropine and those who had received the placebo, 30 min after drug administration and 1 h after return from the operating theatre, but not in trial 4, 3 h after their return.

The treatment groups did not differ on the delayed recall of List 1, which had been presented before drug administration. In the later trials, when hyoscine had affected immediate recall, analyses of delayed recall were carried out, not on the actual number of words recalled on the delayed test, but as a percentage of the number which had been recalled immediately. In trial 3, patients given hyoscine recalled significantly fewer words after the interval between trials 2 and 3 than the placebo group ($P < 0.01$), and in trial 4, they also recalled significantly fewer words after the interval between trials 3 and 4 than the atropine group ($P < 0.01$). Thus, the ability to recall the words again after an interval was impaired for the lists which were presented after drug administration, but not for the list which had been presented before drug administration. This impairment of delayed recall was evident up to the last trial, 3 h after return from the operating theatre.

Choice reaction time. To reduce the effect of chance inattention, any CRT exceeding the mean + two standard deviations were excluded from the analyses. In trial 4, patients who had received hyoscine had significantly slower total CRT than patients in both the placebo and atropine groups ($P < 0.01$) and slower latency CRT than the placebo group ($P < 0.01$). However, when comparing trial 4 with trial 1, both total and latency CRT were significantly slower for patients receiving hyoscine than both the placebo and atropine groups ($P < 0.05$ and $P < 0.01$, respectively). In other words, the difference in performance between the last and the first testing occasions for patients who had received hyoscine was greater than for patients in the other two groups; they were slower both to initiate motor movement and to complete it.

Cancellation test. In trial 3 (1 h after return from the operating theatre) patients given hyoscine were significantly slower to complete this test than those in the atropine and placebo groups ($P < 0.01$), and made significantly greater numbers of errors—that is, missing targets ($P < 0.01$). Comparing trial 3 with trial 2, the hyoscine group were significantly slower than the atropine group ($P < 0.05$). In the last trial, patients who had received hyoscine were still significantly slower than patients in the placebo group ($P < 0.05$) and comparing trial 4 with trial 1, they were significantly slower than patients in both the atropine and the placebo groups ($P < 0.01$). They also made a total of 12 false positive errors in trial 4, while patients in the atropine group made a total of 5, and patients in the placebo group made a total of only 2.

Gibson maze test. In trial 3, patients who had been given hyoscine performed significantly more slowly than patients given the placebo ($P < 0.05$). In trial 4, and comparing trial 4 with trial 1, they also performed significantly more slowly than patients who had received atropine ($P < 0.05$). There were no significant differences between the groups in the number of errors made on any of the comparisons.

DISCUSSION

This study has shown significant differences in the performance of patients between those who had received hyoscine and those who had received atropine or the placebo on certain tests. Moreover, some of the differences were evident still on the last testing occasion—which took place 1–2 h before day-case patients were due for discharge. On the other hand, patients who received atropine and those who received the placebo differed in their performance of only one test 30 min after drug administration (backwards digit span). Wetherell (1980) had found an effect of atropine on volunteers' performance of a forwards digit span test, 1 h after a large dose (2 mg) of atropine i.m., but not on backwards digit span.

Only two out of the six self-rated mood scales, those measuring interest and anxiety, showed that patients given hyoscine were less bored and less anxious than patients who received the placebo. These effects were probably the result of the greater sedative action of hyoscine (Longo, 1966; Shutt and Bowes, 1979). Some authors have suggested that the sedative action of hyoscine is a desirable effect, as it reduces anxiety before the operation (Pandit, Dundee and Keilty, 1971). However, in the present study, the differences on the mood scales were not shown until after the operation. Only one orientation question ("What time is it?") was answered correctly less often by patients who had received hyoscine, again probably as a result of the fact that they were more drowsy after the operation than the other patients and, therefore, less able to notice a clock or to ask the time.

Hyoscine had no effect on the ability to perform simple tasks such as reciting the alphabet or repeating short series of digits. This is in agreement with other studies (Safer and Allen, 1971; Drachman and Leavitt, 1974; Ghoneim and Mewaldt, 1975), in which hyoscine was administered by different routes and in different doses, and in which digit span was tested 1 h after administration. None of these studies tested backwards digit span performance, which was shown to be affected by hyoscine in the present study, suggesting that hyoscine affects the more complex ability to both store and operate on information at the same time. This effect, however, was not evident on the last trial (3 h following operation).

Hyoscine had some effect on the ability to recall meaningful information immediately, which was clearest 30 min after administration, and 1 h after return from the operating theatre. The ability to recall information which had been presented before drug administration, after an interval of about 1 h, was not significantly affected by hyoscine, a finding in agreement with those of Ghoneim and Mewaldt (1975) and Petersen (1977). However, the present study did reveal an impairment, in comparison with atropine and the placebo, of recall after intervals of several hours when the information had been presented while patients were under the influence of the drug, and this effect was apparent even on the last testing occasion. Petersen (1977) found such an effect only with a large (10 μg kg^{-1} i.v.) injection of hyoscine. This study showed, therefore, that hysocine affected information acquisition but, more importantly, it affected retrieval processes when information was presented after the administration of the drug, and this may have implications for anaesthetists giving instructions or other information to patients.

The greatest effect of hyoscine was to slow down motor speed and visuo-motor co-ordination, effects which were apparent for many hours after return from the operating theatre. Some patients given hyoscine complained of blurred vision during the cancellation test 1 h after return from the operating theatre, which may partly account for the greater number of targets which they missed, but none complained of this on the last testing occasion, when the most false positive errors were made. Thus, patients who receive hysocine as a premedication in day-case surgery may still be affected by it at the time of their discharge from hospital.

This study has revealed information about the nature of the cognitive effects of hyoscine, as used in clinical practice, while it has shown that the clinical dose of atropine has minimal effects on cognitive performance compared with a placebo. It raises the question of whether the dose of hysocine used most often in clinical practice (0.4 mg) could be reduced without decreasing its effectiveness as a premedicant. Mirakhur, Dundee and Connolly (1979), however, recommended that the most effective dose of hyoscine i.m., in terms of its antisialagogue action, is 0.5 mg. This study has also shown that the effects of hyoscine on motor functions may last up to the time of discharge from hospital in day-case surgery, which suggests that patients should be informed of the side-effects of hyoscine and that perhaps such information would increase compliance with advice about journeying home.

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NON-VERBAL RESPONSE TO INTRAOPERATIVE CONVERSATION

H. L. BENNETT, H. S. DAVIS AND J. A. GIANNINI

SUMMARY

In a double-blind study, 33 patients (herniorraphy, cholecystectomy and orthopaedic) were randomly assigned to either suggestion or control groups. Under known clinical levels of nitrous oxide and enflurane or halothane anaesthesia, suggestion patients were exposed to statements of the importance of touching their ear during a postoperative interview. Compared with controls, suggestion patients did touch their ear (tetrachoric correlation 0.61, P <0.001) and they did so more frequently (Mann–Whitney U test, P < 0.02). All suggestion patients were completely amnesic for the intraoperative spoken suggestion, despite inquiries which included hypnotic regression to the operation.

There is reason to believe that patients under general anaesthesia can hear. The literature examining the registration of auditory events during anaesthesia falls into physiological and behavioural categories. Auditory evoked responses are maintained under clinical concentrations of inhalation anaesthetics (Clark and Rosner, 1973; Rosner and Clark, 1973). With deeper anaesthesia, auditory responses at the cochlear nucleus increase markedly with response components maintained at the association cortex (Winters, 1976). The consequences of these registrations are difficult to deduce because of the postoperative amnesia which is a sequel of adequate clinical anaesthesia.

Behavioural studies have assessed this amnesia and found it to be quite impenetrable using normal measures of assessing memory. Using stimuli such as letter–word pairs or repetitions of single words (Dubovsky and Trustman, 1976), a poem, a fire bell and a list of words (Lewis, Jenkinson and Wilson, 1973) and music (Brice, Hetherington and Utting, 1970; Brown and Catton, 1973), both recall and recognition measures have revealed the amnesia familiar to those who have questioned convalescent surgical patients and led to the conclusion that discussion of clinical aspects of the patient's case need not be curtailed in the operating suite (Dubovsky and Trustman, 1976).

Other studies question this advice. Given registration of auditory events at the association cortex, research presenting neutral material may not impact upon the anaesthetized nervous system in the same way as material which is more meaningful to the patient undergoing surgery (Trustman, Dubovsky and Titley, 1977). Levinson's (1965) study examined this issue by staging a "mock" surgical crisis when, by EEG criteria, patients were in Stage III (deep) anaesthesia. Electroencephalographic changes indicating cortical arousal accompanied the crisis in three out of 10 patients. None of the 10 patients recalled the event, although in hypnosis four other patients claimed to. The patients with EEG changes became anxious during the hypnotic session and terminated their own hypnosis. Another study claimed highly therapeutic benefits from presenting positive suggestions addressed personally to the anaesthetized surgical patient (Hutchings, 1961).

This present report describes a double-blind study of postoperative response to intraoperative suggestions given to clinically anaesthetized surgical patients. The findings demonstrate a potential for

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reaction to personally meaningful operating room conversation. The reaction following surgery was non-verbal and was accompanied by complete amnesia. Consistent with the physiological literature on anaesthetic action, cortical areas of language understanding are relatively unaffected compared with midbrain and reticular structures. The finding may have relevance for the content of intraoperative conversation.

PATIENTS AND METHODS

Thirty-three patients from two university teaching hospitals were recruited for the study with Human Subjects Committee approval. Patients presenting for repair of an inguinal hernia ($n = 13$), removal of gall bladder ($n = 12$) and orthopaedic procedures ($n = 8$) participated. The interview with the patient before surgery explained that, throughout the operative procedure, patients would receive over headphones at a normal listening volume, one of two conditions: either a prerecorded tape or the actual operating room sounds and voices. An interview following the procedure would determine their memory, and would involve hypnosis as a possible aid to memory.

Standard anaesthetic practices were followed in all patients. This study was intended as a clinical investigation. As such, there was no interference with premedication or anaesthesia as assessed and administered by the anaesthetist, who operated totally independently. Induction of anaesthesia with thiopentone was followed by nitrous oxide and enflurane or halothane. Neuromuscular blocking drugs were administered to all patients. All medical personnel remained blind to the conditions in effect for all patients and were not involved with the study. All the anaesthetists were asked at the conclusion of the case if the patient had been "aware" during any portion of the procedure. No patient was reported by the anaesthetist to have been aware during the time following induction until emergence. Additionally, in the study reported here, records of vital signs showed no unusual deviations apart from those induced by surgical stimulation.

The assistant operating the tape recorder in the operating room had no other contact with that patient, nor with other members of the research team until after the postoperative interview. Even then, blind conditions were enforced until completion of the study.

Following the induction of anaesthesia, headphones were placed over the patient's ears. In the *control* condition (presenting actual operating room sounds) stereo microphones located in the outer shell of the earphones recorded these events while the earphones delivered them to the ears at the ambient volume. In the *suggestion* condition, a prerecorded tape was played at low volume. Beginning with the initial incision, the tape played continuously, suggesting rapid postoperative healing interspersed with music and songs. In order that patients would recognize it, the voice reading the message belonged to the presurgical interviewer. The 2-h tape was stopped 5 min before beginning reversal of anaesthesia if the surgery lasted less than 120 min; if surgery exceeded 2 h, the tape was started again from the beginning.

A special 3 min personal message was taped by the same individual who interviewed the patient and obtained consent for the study. It was played only for suggestion condition patients and then only once, approximately 5 min before beginning the reversal of anaesthesia. This message by a familiar voice was designed both to increase the effectiveness of intraoperative events by personally addressing the patient and stating the patient's postoperative goals, and to suggest that a certain specific behaviour should occur during the convalescent interview. This suggestion stated, "(Patient's preferred name), when I come and talk with you, it is very important that you pull on your ear so that I can know you have heard this. When I come to talk with you, you will pull on your ear. Your ear might itch a little and you will need to pull on it, or you might just know to pull on your ear. That way I will know you have heard this." The importance of the behaviour was again emphasized, ". . . so that doctors and nurses will know that you can hear in surgery."

The suggestion allowed for a non-verbal response to intraoperative statements. If patients respond to the suggestion with spontaneous observable behaviour during the "blind", postoperative interview, support is thereby provided for the potentially suggestive effect of intraoperative conversation. On the other hand, if patients do not respond, the amnesia may be the result of an inability of the nervous system to comprehend or store verbal input while under the influence of general anaesthetic agents.

Assignment to *suggestion* group or to the operating room sounds *control* group was random by a 2:1 ratio (control $n = 22$, suggestion $n = 11$). The two samples otherwise did not differ from each other by age, weight or general physical condition. All were ASA

I or II, with no known mental disease.

The postoperative interview was conducted at least 2 days after the operation. One member of the two-person interview team was always the investigator who had obtained the patient's consent and whose voice was on the suggestion tape; both members were "blind" to the operating room condition. The interview was standardized and contained five structured parts developed in a previous pilot study. (1) It assessed present status and all memories for the perioperative period. This was followed by (2) assessment of ability to be hypnotized utilizing a standardized scale, the Stanford Hypnotic Clinical Scale involving an induction of hypnosis followed by five hypnotic suggestions: (a) motor automatism, (b) a hypnotic dream, (c) age regression to elementary school, (d) a posthypnotic suggestion, and (e) amnesia for the suggested scale items (Hilgard and Hilgard, 1979). Following this assessment and with the patient in the waking state there was (3) a discussion of the Scale with the patient and of the patient's willingness to proceed with the specialized hypnotic regression to the operation. Through a special programme based on dissociation theory (Hilgard, 1977) and using clinical hypnotic techniques, there followed (4) a hypnotic regression to the operation, with strong suggestions that memories for events during surgery would become conscious. Finally, (5) a discussion and debriefing ended the interview.

Being "blind" to the events during a patient's surgery, the interviewers did not bias the suggestion or control groups. All ear touching took place during non-hypnotic portions of the interview and was reliably observed by the interview team ($r = 0.92$).

RESULTS

Thirty-two of the 33 patients were interviewed; one control patient could not be interviewed.

Spontaneous verbal memory

Patients could not remember anything from the period following induction of anaesthesia until awakening in the recovery room or on the ward. This coincides with a reported incidence of less than 1% for conscious memories following anaesthesia, such recall being interpreted as the result of insufficient depth of anaesthesia (Hutchinson, 1960). By standard criteria, patients in our study demonstrated the post-anaesthetic amnesia which usually accompanies adequate general anaesthesia.

Non-verbal memory

Nine of the 11 suggestion patients showed at least one ear touch during the interview, as did nine of the 21 control patients. Table I gives the relevant data for the suggestion group, including the CNS-active anaesthetics they were receiving at the time of the suggestion. An exact 2 × 2 frequency table of the number of patients in each group who touched their ear produces Fischer's exact $P = 0.05$. This represents a tetrachoric correlation between specificity of response and group of 0.61 ($P < 0.001$). A further finding (fig. 1) was the difference in attention paid to the ear, which was significant by a Mann–Whitney U test ($U = 49$; $n_1n_2 = 231$; $P < 0.02$). Patient behaviour was therefore significantly affected by verbal statements made during general anaesthesia, although there was a complete conscious amnesia for the precipitating event under anaesthesia. No suggestion patient recalled the ear touching suggestion during any portion of the interview.

Memory under hypnosis

When regressed under hypnosis back to the operation, none of the 11 suggestion patients could recall the ear touching suggestion. This lack of retrievable memory, even in hypnosis, confirms the dense post-anaesthetic amnesia, but it is a retrieval failure rather than one of memory formation. This is deduced from the fact that the ear touching suggestion was clearly successful, although attempts at retrieving the memory of the suggestion were not.

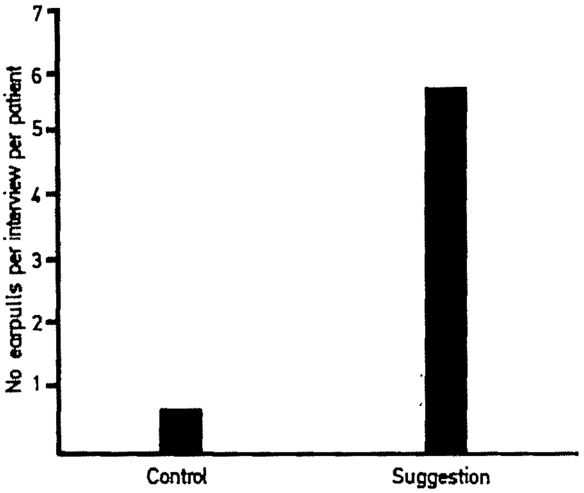

FIG 1. Behavioural responses of patients in double-blind interview. Suggestion condition: nine of 11 patients showed ear pulls for a total of 66 earpulls for 655 s. Control condition: nine of 21 patients showed earpulls for a total of 18 earpulls for 98 s. Mann–Whitney U test: $P < 0.02$.

TABLE I. *Non-verbal responses to intraoperative suggestion made during postoperative interview. C = cholecystectomy, H = inguinal herniorraphy, O = orthopaedic procedures on the leg. †Anaesthetic concentrations in effect at time of suggestion for postoperative ear touching. ‡Total time of hand to ear contact. *Stanford Hypnotic Clinical Scale: increasing hypnotizeability scored 0–5*

Patient	Sex	Age (yr)	Ht (cm)	Wt (kg)	Op.	Premedication	Anaesthetic†	No. ear touches	Time‡ (s)	SHCS*
1	F	24	162	79	C	Meperidine 50 mg+ glycopyrrolate 0.4 mg+ droperidol 5 mg+ hydroxyzine 75 mg	50% N_2O + 0.5% enfl.	1	15	3
2	F	50	165	109	C	Morphine sulphate 5 mg	50% N_2O + 0.6% hal.	2	2	1
3	F	39	175	68	C	Meperidine 75 mg+ hydroxyzine 50 mg	67% N_2O + 1% enfl.	1	1	4
4	M	40	170	63	C	Meperidine 75 mg+ hydroxyzine 75 mg	67% N_2O + 0.5% enfl.	17	300	3
5	F	35	160	80	C	Morphine sulphate 8 mg+ glycopyrrolate 0.2 mg+ droperidol 5 mg	60% N_2O	9	25	4
6	M	38	178	66	H	Meperidine 25 mg+ alphaprodine 20 mg+ hyoscine 2 mg+ perphenazine 2 mg+ droperidol 5 mg	67% N_2O	0	0	4
7	M	22	175	86	O	Morphine sulphate 8 mg+ hydroxyzine 100 mg	67% N_2O + 3% enfl.	0	0	0
8	F	22	165	49	H	Morphine sulphate 5 mg+ hydroxyzine 75 mg	67% N_2O + 1.25% enfl.	6	6	5
9	M	32	181	120	H	Meperidine 100 mg+ droperidol 5 mg	67% N_2O	14	14	4
10	M	32	183	82	H	Morphine sulphate 8 mg+ glycopyrrolate 0.3 mg+ hydroxyzine 100 mg	67% N_2O + 0.75% enfl.	4	4	1
11	M	19	165	68	H	Pentobarbitone 100 mg	67% N_2O + 0.25% hal.	12	300	2

Despite the amnesia for the non-verbal suggestion, there were several examples in both suggestion and control groups of verifiable memory under hypnosis for intraoperative events. We provide two here and a fuller report is forthcoming. Patient 7 (table I) was a 22-yr-old Hispanic male who was not suggestible by the hypnotic assessment scale and he did not respond to the ear touching suggestion he received. However, from within his own self-generated hypnotic trance, he recalled the composer and musician of a taped selection played just before the ear touching suggestion. He was at the same level of anaesthesia for both events and, although clearly not suggestible, recalled, "a male voice speaking to me, telling me to relax" and "soothing music by Chuck Mangione, the same that I hum to myself". This man had a high anaesthetic requirement—3% enflurane with nitrous oxide and oxygen.

Another occurrence of apparent hypnotic recall was in the control group, from a 35-yr-old white female having a bone graft to her femur. At 40 min into a 205-min operation, with the patient receiving 50% nitrous oxide and 1% enflurane, the surgeon said, "We've (*sic*) got this all goof-balled here, didn't we . . . this is going to be a terrible bone graft. It's going to be the worst bone graft ever . . . this is going to be awful." In the double-blind interview, and in hypnosis, the patient recalled that something was wrong and, with further probing, "my leg, it's not going to work right. The doctor said it wasn't going to work the way it should." Of our total study sample, only this patient was exposed to such a pessimistic remark in surgery. She had by far the longest convalescence of the 33 patients, requiring a total of 72 pain medications over her 14-day convalescence, twice that of the next demanding orthopaedic patient. A recent report (Weinberger, Gold and Sternberg, 1984) using rats showed strong aversive conditioning 2 weeks after white noise was paired with shock under deep chloral hydrate–pentobarbitone anaesthesia. During conditioning under anaesthesia, neither the ECG or the EEG showed changes from baseline values. The patient exposed to the pessimistic remark may have responded at a non-verbal level involving affective and autonomic systems, leading to a protracted recovery.

DISCUSSION

Through double-blind methods, this study asked if there might be a dissociative reaction to the suggestive content of operating room voices acting as a form of learning. The criterion of standard post-anaesthetic verbal amnesia was maintained while non-verbal behaviour (ear pulling) indicated learning of intraoperative events. Criticisms of this study might include the lack of a formal assessment of anaesthetic depth by end-tidal gas analysis or by the EEG. With controlled laboratory studies utilizing these indices showing registration of auditory events at the cortex under surgical concentrations of inhalation anaesthetics, the relevant issue for us was the nature of the postanaesthetic amnesia under usual clinical conditions. In studies of other amnesias, both organic and functional, it is apparent that amnesic patients, when appropriately probed, can often recall as much as do normal subjects, although free recall through spontaneous verbal memory is severely depressed.

In reviewing studies of learning during natural sleep, Evans (1979) has shown that linguistic messages can influence both sleep mentation and dreams as well as sleep behaviour. In one study, a suggestion to make a specific movement during sleep was given during Stage 1 REM sleep. The suggestion was paired with a cue word as a hypnotic suggestion. The word alone elicited the behaviour during later REM periods and, interestingly, over later nights of sleep. All subjects, however, were amnesic for the messages in the waking state, yet the verbally cued behaviour persisted during sleep. One subject showed behavioural responding 5 months after the original learning trial.

Adam (1979) has experimentally assessed verbal and non-verbal memory following exposure to sub-anaesthetic doses of inhalation agents. Test trials after recovery from anaesthesia showed performance which gradually increased in accuracy over 1 week. Thus, the recovery of memory over time following sub-anaesthetic exposure indicates that "the data do not support the expectation that general anaesthetics affect to a significant degree basic neurophysiological processes involved in memory formation such as memory trace decay or consolidation of traces."

In reviewing the research of both functional and organic amnesias, Hirst (1982) cited studies with humans which indicate that verbal recall is not sufficient to assess memory for earlier motor and verbal learning trials. Our results from the operating room environment support these findings for post-anaesthetic amnesias.

The data in the present study establish the phenomenon of a non-verbal response to intraoperative conversation. The data show that the conscious amnesia required for clinically adequate anaesthesia is not a sufficient indicator of lack of responsiveness to operating room voices. The reaction may be entirely non-verbal, involving systems not accessible to ordinary memory retrieval. Language comprehension is a highly practised skill. The automatic nature of comprehending spoken language may continue at a neural level during states of surgical anaesthesia. Studies designed to assess awareness, perception, learning or memory during anaesthesia must utilize methods which are sensitive to known mechanisms of amnesia and neuropharmacology. We might expect the nervous system to remain responsive to pertinent linguistic messages during anaesthesia, although verbal recall will ordinarily be suppressed.

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COMPARISON OF THE OCULAR EFFECTS OF ATROPINE OR GLYCOPYRROLATE WITH TWO I.V. INDUCTION AGENTS

J. GREENAN AND J. PRASAD

SUMMARY

Atropine and glycopyrrolate combined with either methohexitone or thiopentone were compared with the induction agent alone in patients undergoing electroconvulsive therapy. Patients acted as their own controls in each sub-group defined by induction agent. Pupil size, muscle twitches, presence of hiccups and the extent of oropharyngeal secretions were noted. Methohexitone produced a greater and more prolonged increase in pupil size than did thiopentone. The subsequent pupil size following the atropine–methohexitone mixture was significantly greater than that following the glycopyrrolate–methohexitone mixture. The combination of atropine with thiopentone produced a greater "secondary" mydriasis than thiopentone alone, or thiopentone combined with glycopyrrolate. The effect of the glycopyrrolate–thiopentone combination did not differ significantly from that of thiopentone alone. Methohexitone was associated with a greater incidence of hiccups, muscle twitching and excessive salivation.

Patients undergoing routine outpatient anaesthesia for electroconvulsive therapy (ECT) frequently receive anticholinergic premedication i.v. to protect against vagal reflexes resulting from either the electroconvulsive shock (Dobkin, 1958) or the administration of suxamethonium i.v. Some of these patients complain of difficulty in focusing once the procedure has been completed.

The present study compared the effects of thiopentone or methohexitone on pupil size, and examined the effect of the two anticholinergic agents, atropine or glycopyrrolate, given concomitantly with either induction agent.

PATIENTS AND METHODS

Forty-eight healthy patients about to undergo electroconvulsive therapy (ECT) took part in the study. The patients were divided into two groups of 24 according to the induction agent administered: methohexitone 1.3 mg kg^{-1} or thiopentone 4 mg kg^{-1}.

Each patient attended the clinic on three separate occasions. At each of these visits they received i.v., with the anaesthetic, one of the following three study drugs: atropine 0.6 mg, glycopyrrolate 0.2 mg or saline. The drugs were administered "double-blind" and the order of administration was completely balanced. The injection was given over a period of 20 s to a large vein at the cubital fossa. Many of the patients were concomitantly receiving psychotropic drugs. Their drug therapy did not change during their participation in this study.

Pupil size, measured by a pupilometer, was recorded immediately before the administration of the induction mixture, and at 1, 2, 4, 5, 10, 30 and 60 min following induction. All measurements of pupil size were carried out under the same ambient lighting conditions. Suxamethonium 50 mg was administered after the 1-min assessment. The electric shock was delivered immediately after the 2-min assessment. Oropharyngeal secretions were recorded on a three-point scale: dry, moist or unacceptably wet, before induction, and at 10 and 30 min following induction. The presence or absence of pain on injection, and the occurrence of hiccups or muscle twitching following injection, were noted.

Comparison of data within patients was carried out using analysis of variance and paired *t* test. Comparison of data between the two different

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TABLE I. *Demographic details of the patients studied (mean values ± SEM)*

Induction agent	Number	Male	Age (yr)	Weight (kg)
Methohexitone	24	10	46 ± 3.4	65 ± 3.0
Thiopentone	24	7	51 ± 3.6	66 ± 2.2

anaesthetic groups utilized the two-sample *t* test. Non parametric data were analysed by the Chi-squared test. Statistical significance was taken as a *P* value of less than 0.05.

RESULTS

The demographic data on the patients participating in this study are shown in table I. The patients were well matched with regard to age, weight and sex distribution.

Methohexitone induction

Induction of anaesthesia with methohexitone alone produced a rapid and statistically significant increase in pupil size. The increase noted at 1 min was not modified by the incorporation of either atropine or glycopyrrolate (table II and fig. 1). Pupil size decreased after 2 min at all three visits but, surprisingly, the pupil size was still significantly enlarged 60 min following induction with methohexitone alone. There were no significant differences in pupil size when atropine and methohexitone were used compared with those observed after the administration of methohexitone alone. The combination of glycopyrrolate with methohexitone was associated with a smaller pupil size at all times compared with those patients receiving methohexitone alone. The atropine-containing mixture produced statistically significantly greater increases in pupil size than the glycopyrrolate-containing mixture at 2, 10 and 60 min. In addition to the differences in the mean pupil size, there was also a difference in the number of patients with an increase in pupil size of greater than 2 mm (table III). The differences between atropine and glycopyrrolate were particularly evident from 10 min onwards.

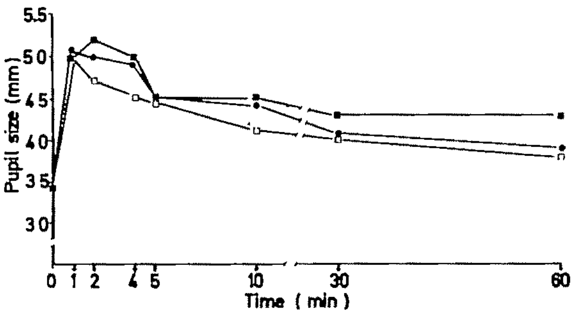

FIG 1. Mean pupil size following administration of methohexitone with □ glycopyrrolate, ■ atropine, ● saline.

TABLE II. *Pupil size (mean values ± SEM)*

	Time (min)							
Group	Pre ind.	1	2	4	5	10	30	60
Methohexitone with:								
Placebo	3.4 ±0.15	5.1 ±0.25	4.9 ±0.24	4.9 ±0.19	4.5 ±0.17	4.4 ±0.15	4.1 ±0.15	3.9 ±0.18
Atropine	3.4 ±0.15	5.0 ±0.27	5.2 ±0.22	5.0 ±0.22	4.5 ±0.16	4.5 ±0.17	4.3 ±0.21	4.3 ±0.22
Glycopyrrolate	3.4 ±0.13	5.0 ±0.30	4.7 ±0.22	4.5 ±0.22	4.5 ±0.24	4.1 ±0.19	3.9 ±0.18	3.8 ±0.18
Thiopentone with.								
Placebo	3.2 ±0.12	3.8 ±0.23	3.4 ±0.22	3.6 ±0.18	3.6 ±0.20	3.5 ±0.25	3.5 ±0.25	3.4 ±0.19
Atropine	3.2 ±0.14	3.9 ±0.28	3.6 ±0.20	4.0 ±0.22	4.1 ±0.25	4.1 ±0.22	4.1 ±0.22	4.0 ±0.17
Glycopyrrolate	3.1 ±0.15	4.0 ±0.27	3.5 ±0.21	3.8 ±0.19	3.8 ±0.16	3.7 ±0.21	3.5 ±0.24	3.3 ±0.18

Thiopentone induction

Pupil size increased within 1 min after the administration of the three thiopentone-containing mixtures. Following this, the mydriasis decreased following thiopentone alone. The pupil size then increased following this initial decrease (table II; fig. 2). The magnitude of this "secondary" increase was greater when atropine was used. Statistically significant differences were noted between the responses to atropine–thiopentone and thiopentone alone from 4 to 60 min. In contradistinction, the increase elicited by the concomitant administration of glycopyrrolate was not significantly different from that produced by thiopentone alone. Significant differences were noted between the atropine–thiopentone and glycopyrrolate–thiopentone responses at 30 and 60 min. The number of patients with an increase in pupil size of greater than 2 mm is shown in table III.

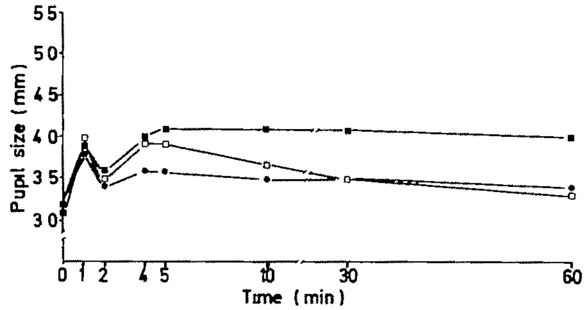

FIG 2. Mean pupil size following administration of thiopentone with □glycopyrrolate, ■ atropine, ● saline.

Differences between methohexitone and thiopentone

Changes in pupil size. Methohexitone alone produced greater mydriasis than did thiopentone alone. This difference was statistically significant from 1 to 10 min after administration (fig. 3).

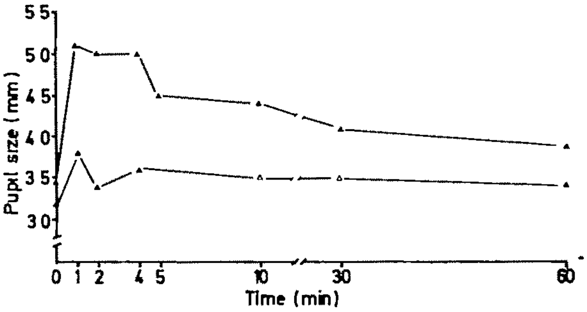

FIG 3. Mean pupil size following administration of ▲ methohexitone alone and △ thiopentone alone.

Atropine in combination with methohexitone produced significantly greater increases in pupil size than atropine combined with thiopentone at 1–4 min. The response to the glycopyrrolate–methohexitone combination was significantly greater than the response to the glycopyrrolate–thiopentone mixture at the 2-min period only.

Other variables. Only one patient (receiving atropine with methohexitone) complained of pain on injection. Hiccups were reported on four occasions (in four different patients) following induction with methohexitone. There were many more occurrences of muscle twitching with methohexitone. Twitching was recorded in 32% of the patients in whom induc-

TABLE III. *Number of patients with increase in pupil size of greater than or equal to 2 mm. *Significantly greater than glycopyrrolate* ($P < 0.05$), *†significantly greater than placebo* ($P < 0.05$)

	Time (min)						
Group	1	2	4	5	10	30	60
Methohexitone with:							
Atropine	11	9	9	6	8	5	6*
Glycopyrrolate	8	8	6	6	4	1	1
Placebo	11	8	8	7	5	3	2
Thiopentone with.							
Atropine	4	3	5†	6†	6*†	5	3
Glycopyrrolate	4	2	4	3	1	2	0
Placebo	4	1	0	0	1	2	0

tion was carried out with methohexitone, compared with only 6% with thiopentone. Anticholinergic administration did not alter the occurrence of twitching, which was similar in all three groups. Excessive secretions were recorded in 13% of the patients when thiopentone alone was used and in 29% when methohexitone alone was used. This was higher than the number of patients presenting with excessive secretions when the anticholinergics were also administered (4% and 10% for thiopentone and methohexitone, respectively). There was no difference between atropine and glycopyrrolate in the control of oropharyngeal secretions.

DISCUSSION

The present study has shown that the induction of anaesthesia with methohexitone was associated with a greater and more prolonged increase in pupil size than was induction using thiopentone. In addition, the incidence of hiccups, muscle twitching and excessive salivation was greater when induction was with methohexitone.

Patients undergoing short duration anaesthesia in which atropine has been used sometimes complain of difficulty in focusing. It was not considered appropriate to study visual accommodation in our patients, because of their psychiatric history. Thus, pupil size was used as an index of the "ocular" effects of the drug combinations. The data show quite clearly that both thiopentone and methohexitone produced mydriasis, but that the effect of thiopentone alone was transient, whereas that of methohexitone was prolonged, significant effects existing for up to 60 min after administration. The combination of atropine with thiopentone resulted in the development of a "secondary" mydriasis, the effect of which was still significant 60 min after administration. In contrast, glycopyrrolate had no prolonged secondary effect on pupil size. The pupil size after the administration of the glycopyrrolate–methohexitone combination was less than that following the anaesthetic agent alone. In addition, the pupil sizes were significantly less than those measured after the atropine–methohexitone combination. These results suggest, albeit indirectly, that patients undergoing anaesthesia of short duration, and who are receiving glycopyrrolate at induction, will have fewer problems with accommodation than those receiving atropine, irrespective of the induction agent used.

Criticism may be made of the doses chosen in this study. Glycopyrrolate has been shown to be from two (Mirakhur, Jones and Dundee, 1981) to five (Mirakhur, Dundee and Jones, 1978) times as potent as atropine, depending upon the response measured. However, the object of the present study was to compare the effects of the dose of atropine currently used in this centre with the dose of glycopyrrolate currently used and recommended by the manufacturers.

There are few published data on the effect of methohexitone and thiopentone on pupil size. The prolonged mydriasis produced by methohexitone is surprising. Its mechanism is not clear, but the effect does not follow the time course of this drug on the central nervous system. Once the initial effects of the induction agents have diminished, the mydriatic actions of atropine become noticeable. It is evident from the present study that it takes approximately 5 min for the full effect of atropine to become established. Thereafter, the pupil remains dilated for a considerable period of time. The lack of effect of glycopyrrolate on the eye is consistent with the findings of Mirakhur, Dundee and Jones (1978) who showed that, in conscious volunteers, doses of up to 0.2 mg i.v. had no effect on pupil size or visual accommodation. The same group showed, in addition, that atropine 0.5–2.0 mg i.m. had pronounced effects on both these indices, whereas glycopyrrolate 0.1–0.4 mg had no such effects (Mirakhur and Dundee, 1980).

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COMPARISON BETWEEN GLYCOPYRROLATE AND ATROPINE IN A MIXTURE WITH NEOSTIGMINE FOR REVERSAL OF NEUROMUSCULAR BLOCKADE

Studies in patients following open heart surgery

M. G. SALEM, J. C. RICHARDSON, G. A. MEADOWS, G. LAMPLUGH AND K. M. LAI

SUMMARY

Atropine and glycopyrrolate were compared in a mixture with neostigmine for reversal of neuromuscular blockade in patients undergoing open heart surgery. In patients not receiving β-blocking drugs, glycopyrrolate was shown to possess advantages over atropine in terms of a lower initial increase in heart rate, better protection against the muscarinic effects of neostigmine, and smaller increases in rate–pressure product. The concomitant administration of β-adrenergic blocking therapy significantly attenuated the effect of reversal on heart rate and the differences between atropine and glycopyrrolate were not significant. There was no difference in the incidence of arrhythmias between patients who received β-blocking drugs and those who did not.

Clinical studies have demonstrated that the speed of onset of action of glycopyrrolate on the cardiovascular system is slower than that of atropine. As a result, when glycopyrrolate is combined with neostigmine to antagonize residual neuromuscular block, the initial increase in heart rate, seen frequently with a mixture of atropine and neostigmine, is less marked (Cozanitis et al., 1980).

Most of the clinical studies on the use of glycopyrrolate at the time of reversal have involved patients without cardiovascular disease. However, Cozanitis and colleagues (1980) suggested that, in patients with pre-existing cardiovascular dysfunction, the differences between glycopyrrolate and atropine were more marked than those observed in patients with normal cardiovascular function. Furthermore, in a study by Bali and Mirakhur (1980) involving patients undergoing closed mitral valvotomy, atropine with neostigmine was associated with a marked increase in heart rate. However, the increase in heart rate was less in similar patients receiving a mixture of glycopyrrolate and neostigmine.

The present study compared the changes in heart rate, rhythm and arterial pressure after the administration of a mixture of neostigmine and atropine with those obtained following a mixture of neostigmine and glycopyrrolate, in patients undergoing open heart surgery.

PATIENTS AND METHODS

The study was carried out in 40 patients undergoing open heart surgery for valve replacement or coronary artery by-pass grafting.

Exclusion criteria were any condition in which it would be inadvisable to antagonize residual neuromuscular blockade, known hypersensitivity to either atropine or glycopyrrolate and patients who were receiving or who had received, within the 15 min before the reversal of neuromuscular block, a hypotensive agent such as sodium nitroprusside or an inotropic agent such as isoprenaline or dopamine.

Patients received amylobarbitone 200 mg orally the night before operation. One hour before the induction of anaesthesia, droperidol 10 mg was given i.m. Following preoxygenation, anaesthesia was induced with either morphine 20 mg or phenoperidine 2–4 mg and droperidol 10 mg i.v. Pancuronium 8 mg was used to facilitate tracheal intubation. Anaesthesia was maintained with 60% nitrous oxide in oxygen. Increments of pancuronium were given when required. The patient's lungs were ventilated during the operation with an

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East-Radcliffe ventilator. Halothane was used to control arterial pressure before cardiopulmonary bypass and to produce vasodilatation during bypass.

At the end of surgery, and with the patients breathing 50% nitrous oxide in oxygen, a mixture of neostigmine 5.0 mg with either atropine 1.8 mg or glycopyrrolate 0.9 mg was administered as a "bolus" injection i.v. The anticholinergic component of the reversal mixture was administered double-blind. Twenty of the patients were receiving β-adrenergic blocker therapy and 20 were not. Within each of these two sub-groups there was an equal distribution of patients receiving atropine or glycopyrrolate.

The patients remained in the operating theatre for 15 min after the administration of the reversal mixture, following which they were transferred to the intensive care unit. The trachea was extubated and 100% oxygen was given via an anaesthetic oxygen mask.

Heart rate was recorded from the digital display of the monitor. Rhythm changes were noted from inspection of the display. Systolic and diastolic arterial pressures were recorded via an indwelling arterial catheter. Arterial pressure, heart rate and any changes in rhythm were recorded at the following times relative to the administration of the reversal mixture: –1, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 30, 45, 60, 90, 120 min. Rate–pressure product was calculated.

Oropharyngeal suction was performed before extubation and the amount of secretion classified by the attending anaesthetist as being "excessive" or "not excessive".

RESULTS

The physical characteristics and mean baseline heart rates are shown in table I. Considering the small size of this study, the patients were reasonably well matched. The slow mean heart rate in patients taking β-blocking drugs and receiving glycopyrrolate was noted.

Heart rate: patients without β-blockade

The changes in heart rate following the administration of the reversal mixtures are shown in figure 1.

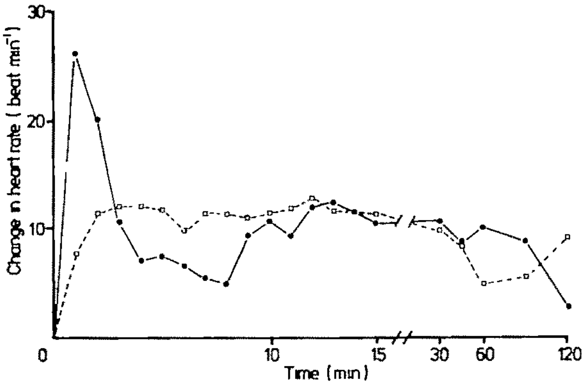

FIG 1. Change in heart rate in patients who were not receiving β-blocking drugs.
● —— ● = Atropine; □ — □ = glycopyrrolate.

Atropine in combination with neostigmine produced a more immediate and marked increase in heart rate than did glycopyrrolate. At 1 min, the differences between the atropine and glycopyrrolate groups were significant (*t* test: $P < 0.01$). Following this initial increase, the heart rates decreased gradually and subsequent values were similar to those in the patients receiving glycopyrrolate.

Heart rate: patients receiving β-blocking drugs

Beta-blockade decreased the effects on heart rate (fig. 2). Whereas in the previous group, reversal produced a statistically significant increase in heart rate on most occasions, in the patients receiving β-blocking drugs, insignificant increases in heart rate followed the administration of both reversal mixtures. There were no significant differences between the atropine and glycopyrrolate groups.

TABLE I. *Physical characteristics of the patients studied (mean data ± SEM). Glyco. = glycopyrrolate*

	Patients receiving β-blocking drugs		Patients not receiving β-blocking drugs	
	Atropine	Glyco	Atropine	Glyco
Age (yr)	51.5 ± 2.6	50.6 ± 2.5	50.5 ± 4.0	51.6 ± 3.7
Weight (kg)	72.1 ± 2.9	76.4 ± 3.2	57.0 ± 8.0	63.7 ± 7.9
Pancuronium (mg)	8.6 ± 0.4	8 8 ± 0.4	8.6 ± 0.84	9.6 ± 0.58
Heart rate before admin. of test drug	81.0 ± 4.3	75.0 ± 4.2	91.0 ± 3.4	83.0 ± 5.4

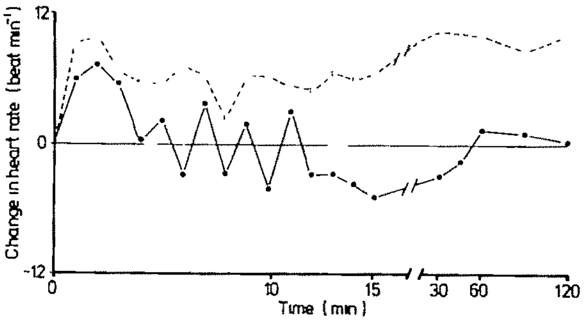

FIG 2. Change in heart rate in patients receiving β-blocking drugs
● —— ● = Atropine, □ — □ = glycopyrrolate

Other cardiovascular variables

Generally, mean systolic and diastolic arterial pressures remained stable following reversal in both groups of patients. Figure 3 shows the mean diastolic arterial pressure in the patients without β-blockade.

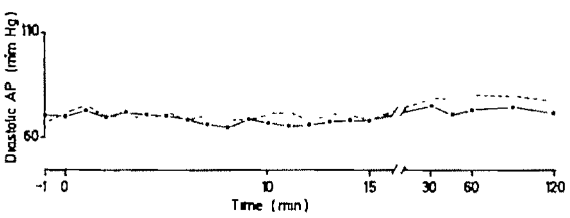

FIG 3. Diastolic arterial pressures in patients who were not receiving β-blocking drugs.
● —— ● = Atropine; □ --- □ = glycopyrrolate.

In the first 5 min following reversal, the rate–pressure products in those patients not receiving β-blocking drugs increased from 11158 to a maximum of 15018 in the patients receiving atropine, and from 10877 to a maximum of 12503 in those receiving glycopyrrolate. Because of the small number of patients, this difference did not achieve statistical significance.

Fifteen of the 40 patients had arrhythmias after reversal. Seven of these had received atropine, and eight glycopyrrolate. There was no difference in the incidence of arrhythmias between patients who were receiving β-blocking drugs and those who were not.

Only two patients had a heart rate of less than 50 beat min^{-1} following reversal; both had received atropine. One of these patients was also receiving a β-blocking drug.

At the time of removal of the trachael tube, six patients who had received atropine had "excessive" oropharyngeal secretions, compared with three patients who had received glycopyrrolate.

DISCUSSION

In patients not receiving β-blocking drugs, glycopyrrolate was associated with a lower initial increase in heart rate, and a smaller increase in rate pressure–product—widely regarded as an index of myocardial oxygen consumption (Clement, 1979; Jones, Knight and Hill, 1980). In this group of patients with severely compromised cardiovascular reserves, a smaller increase in oxygen consumption is a significant clinical advantage.

Our results confirm the stability of heart rate associated with the use of glycopyrrolate as reported previously (Ramamurthy, Shaker and Winnie, 1972; Bali and Mirakhur, 1980; Cozanitis et al., 1980; Mirakhur et al., 1981; Heinonen, Salmenpera and Takkunen, 1982; Kongsrud and Sponheim, 1982). It has been suggested that this stability of heart rate results from the synchronous onset of action of glycopyrrolate and neostigmine, compared with the non-synchronous onset of action of atropine plus neostigmine.

Our results differ slightly from published data, which have generally shown smaller initial increases in heart rate with glycopyrrolate-containing reversal mixtures. Perhaps the dose of glycopyrrolate used here with neostigmine 5 mg was in excess of that actually required. Many of the published data have been obtained from studies using smaller doses of neostigmine and little information exists on the optimum dose to use with neostigmine 5 mg. Another explanation for the differences is that patients who have undergone open-heart surgery are more sensitive to the chronotropic effect of anticholinergic agents. In this respect, it is interesting to note that Bali and Mirakhur (1980) observed only a monophasic response in heart rate following reversal of neuromuscular block with neostigmine–anticholinergic combinations in patients undergoing closed mitral valvotomy.

As might be expected, β-adrenergic blockade decreased the increase in heart rate following the administration of the reversal mixtures. There were no significant differences between the atropine and glycopyrrolate groups in this subgroup of patients.

In this small study, some evidence of the better protection against the muscarinic effects of neostigmine afforded by glycopyrrolate was shown. The incidence of "bradycardia" and unacceptably profuse oropharyngeal secretions was lower when glycopyrrolate was used. These are characteristics which have been the feature of most studies on this anticholinergic at the time of reversal of neuromuscular blockade (Bali and Mirakhur, 1980; Kongsrud and Sponheim, 1982).

As a result of the lack of information on the correct dose of glycopyrrolate for use with neostigmine 5 mg, and bearing in mind the differences between these results and the published results, consideration should be given to the use of a smaller dose of glycopyrrolate.

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Br. J. Anaesth. (1985), 57, 188–191

PATTERN OF CNS RECOVERY FOLLOWING REVERSAL OF NEUROMUSCULAR BLOCKADE

Comparison of Atropine and Glycopyrrolate

S. E. SHEREF

SUMMARY

Recovery from anaesthesia was compared, in a group of patients (n = 25) receiving a mixture of glycopyrrolate and neostigmine (to reverse non-depolarizing neuromuscular blockade), with recovery in a group of patients (n = 25) receiving an atropine–neostigmine mixture. Recovery following anaesthesia was more rapid in the patients receiving the glycopyrrolate–neostigmine mixture.

Glycopyrrolate has been shown to have certain advantages over atropine: when used as an adjunct in the reversal of residual neuromuscular blockade, it is associated with a lower initial increase in heart rate and less secondary bradycardia (Ostheimer, 1977; Mirakhur, Dundee and Clarke, 1977; Cozanitis et al., 1980; Heinonen, Salmenpera and Takkunen, 1982). Moreover, since it is a quaternary ammonium compound, only limited amounts of glycopyrrolate penetrate the blood–brain barrier (Proakis and Harris, 1978) and, as a result, it has no significant central anticholinergic effects.

In a preliminary study, Baraka and colleagues (1980) suggested that arousal from anaesthesia was more rapid in patients receiving glycopyrrolate when compared with a similar group receiving atropine. Heinonen, Salmenpera and Takkunen (1982) demonstrated that, when residual neuromuscular blockade was antagonized with a glycopyrrolate–neostigmine mixture, return of consciousness was more rapid than in a similar group of patients who had received an atropine–neostigmine combination.

We have studied the pattern of recovery of central nervous system (CNS) function in patients in whom residual neuromuscular block was antagonized with a mixture of neostigmine and either atropine or glycopyrrolate.

PATIENTS AND METHODS

Fifty adult patients (ASA Grade I or II) undergoing general surgical or gynaecological procedures took part in the study. Any patient receiving, at the time of the study, phenothiazines, butyrophenones, monoamine oxidase inhibitors, tricyclic antidepressants or any atropine-like drugs, was excluded from the study, as were patients with a known psychiatric history.

Pre-anaesthetic medication consisted of papaveretum 0.2–0.3 mg kg^{-1} i.m., depending on the individual patient, approximately 60 min before the start of surgery. Anaesthesia was induced with a sleep dose of thiopentone 3–4 mg/kg body weight; intubation of the trachea was performed immediately after the administration of either suxamethonium 1 mg kg^{-1} or 2–3 min after the administration of pancuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with 70% nitrous oxide in oxygen from a high-flow open circuit (Cape Waine ventilator), with a minute volume of 150 ml/kg body weight. Tidal volume was measured periodically (Wright's respirometer). Incremental doses of pancuronium 0.02 mg kg^{-1} or papaveretum 5 mg, or both, were administered when necessary. The last incremental dose was given 30 min before the end of surgery. Halothane 0.5%, whenever used, was discontinued approximately 15–20 min before the anticipated end of surgery.

At the end of surgery, and before withdrawal of the nitrous oxide, the patients received a mixture of neostigmine methylsulphate 3.75 mg with either glycopyrrolate 0.6 mg or atropine 1.2 mg. The anticholinergic component of the mixture was administered "double-blind" from specially pre-

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pared coded ampoules, the order of administration being randomized. Nitrous oxide was discontinued after administration of the reversal mixtures. As soon as the patient opened his eyes, oropharyngeal toilet was performed, the tracheal tube removed, and the patient transferred to the recovery ward.

Patients were assessed by the investigator before the induction of anaesthesia, and questioned about their name and exact date of birth, which served as a baseline for the post-anaesthetic pattern of CNS recovery. They were also questioned at the following times after administration of the reversal mixtures: 5, 10, 15, 20, 25, 30, 40, 50, 60 and 120 min. The five-point scoring system used is shown in table I and is a modification of that described by Bidwai, Cornelius and Stanley (1976). Patients who complained of pain following surgery received papaveretum i.m.

TABLE I. *Post-anaesthetic CNS recovery scoring system*

Level	Description
0	Well orientated and initiates conversation
1	Orientated, feels drowsy or falls asleep Gives exact date of birth
2	Disorientated Responds to verbal and painful stimuli Does not give EXACT date of birth (some dissociation)
3	Disorientated Responds to painful but not to verbal stimuli Does not give exact date of birth (in a state of complete dissociation from surroundings)
4	Unresponsive to verbal or painful stimuli No signs of respiratory depression and adequate reversal of muscle blockers

The CNS scores were analysed using the Chi-squared test.

RESULTS

Both groups were similar in regard to age, weight, ASA status and duration of anaesthesia (table II).

The distribution of CNS scores at all times of assessment following reversal is shown in table III. The main differences between atropine and glycopyrrolate occur from the 10th minute onwards. There was a significantly greater number of patients in the glycopyrrolate group with a score of 0 at 15–120 min inclusive (except at 60 min) (table III). The only patient who consistently presented with a score of 2 was a patient who had received atropine in the reversal mixture. There were no patients with a score of 3 in either study group.

TABLE II. *Physical characteristics of the patients in the study (mean values (± SEM))*

	Atropine	Glycopyrrolate
No of patients	25	25
Age (yr)	47.6 ± 2.48	40.0 ± 2.40
Weight (kg)	61.4 ± 2.62	66.6 ± 2.42
Physical status		
ASA I	20	20
ASA II	5	5
Sex		
Male	5	7
Female	20	18
Median duration of anaesthesia (min)	98.3	95 6

Several of the patients received postoperative analgesia in the first 60 min after reversal, and it was considered that this analgesic (papaveretum) could have influenced the CNS score by virtue of its analgesic–sedative effect. Accordingly, a separate analysis was made of the 34 patients who did not receive postoperative analgesia in the first 60 min (17 patients in each group). Figure 1 shows the CNS scoring pattern for these patients. Significant differences were noted between the two groups, at 10, 20, 40, 50 and 120 min ($P < 0.05$).

DISCUSSION

The problems of "somnolence" and "disorientation" following anaesthesia have been recognized for some time, and atropine has been considered responsible (Longo, 1966; Greene, 1971; Lapan and Smith, 1977; Smith et al., 1979). However, few controlled studies have been carried out to test this hypothesis.

At 2 h after operation, the number of patients with a score of 0 (table III) was significantly higher in the glycopyrrolate group. Thus, although atropine does have a short duration of action peripherally, it may have a longer duration of action centrally or, at least, its central after-effects may last longer than was appreciated previously. This observation may have clinical implications, especially if atropine is prescribed for day-case surgery. Further studies are needed to test this.

The central anticholinergic syndrome was first appreciated by Longo (1966). The syndrome consists of confusion, hallucination, agitation, somnolence, delirium, convulsions and decreased ability to

TABLE III. *Post-anaesthetic CNS recovery pattern at various times: number of patients scoring 0, 1, 2 or 4. (No patient presented with a score of 3 in either study group.) Significantly greater than atropine group:* * $P < 0.05$, ** $P < 0.01$

	Atropine group (n = 25)				Glycopyrrolate group (n = 25)			
Time (min)	(0)	(1)	(2)	(4)	(0)	(1)	(2)	(4)
5	4 (16%)	13 (52%)	7 (28%)	1 (4%)	9 (36%)	13 (52%)	2 (8%)	1 (4%)
10	5 (20%)	17 (68%)	3 (12%)	0	11 (44%)	14 (56%)	0	0
15	4 (16%)	19 (76%)	2 (8%)	0	10* (40%)	15 (60%)	0	0
20	3 (12%)	21 (84%)	1 (4%)	0	12* (48%)	12 (48%)	1 (4%)	0
25	5 (20%)	19 (76%)	1 (4%)	0	13* (52%)	12 (48%)	0	0
30	5 (20%)	19 (76%)	1 (4%)	0	14* (56%)	11 (44%)	0	0
40	4 (16%)	20 (80%)	1 (4%)	0	16** (64%)	9 (36%)	0	0
50	4 (16%)	20 (80%)	1 (4%)	0	13* (52%)	12 (48%)	0	0
60	6 (24%)	19 (76%)	0	0	14 (56%)	11 (44%)	0	0
120	9 (36%)	16 (64%)	0	0	20* (80%)	5 (20%)	0	0

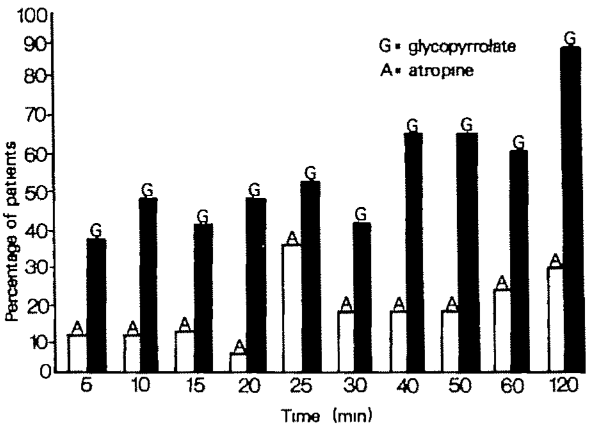

FIG 1. Percentage of patients who had not received postoperative analgesia in the first 60 min with a CNS score of zero at each assessment time.

concentrate (Longo, 1966; Bidwai, Cornelius and Stanley, 1976). The syndrome is triggered by various drugs that exhibit central anticholinergic activity, including atropine (Greene, 1971; Lapan and Smith, 1977; Smith et al., 1979), hyoscine (Longo, 1966), phenothiazines (Bernards, 1973), tricyclic antidepressants (Burk, Walton and Rumack, 1974), thalamonal (Innovar) (Bidwai, Cornelius and Stanley, 1976), butyrophenones (Duvoisin and Katz, 1968), and ketamine (Hill, Stanley and Sentkar, 1977). Since these different groups of drugs are unrelated pharmacologically, it has been assumed that the centrally-acting anticholinesterase, physostigmine, which is used to reverse this syndrome, acts by non-specific mechanisms (Greene, 1971; Bidwai, Cornelius and Stanley, 1976; Hill, Stanley and Sentkar, 1977).

Electrophysiological studies confirmed that central cholinergic pathways are potentiated by physostigmine and depressed by atropine and general anaesthetics (Kinjevic, 1967). Two mechanisms have been suggested: either a decreased sensitivity to acetylcholine during deep general anaesthesia, or a decrease in acetylcholine release (MacIntosh and Oborin, 1953; Mitchell, 1963).

Since glycopyrrolate is a quaternary ammonium compound, it penetrates minimally through the blood–brain barrier (Proakis and Harris, 1978). Therefore, it can be assumed that glycopyrrolate does not affect the acetylcholine pathway in the brain. This may be the explanation why, in this study and in previous work (Baraka et al., 1980; Heinonen, Salmenpera and Takkunen, 1982), arousal from anaesthesia was significantly more rapid in the patients in the glycopyrrolate groups compound, it penetrates minimally through the

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CLINICAL ACTIONS OF FENTANYL AND BUPRENORPHINE

The Significance of Receptor Binding

R. A. BOAS AND J. W. VILLIGER

Opioid analgesic drugs are used with increasing frequency during surgical anaesthesia to control the endocrine and metabolic responses to stress (Hall, 1980). Fentanyl, one of the more effective agents in this respect, is a lipid-soluble agonist of high intrinsic activity with ready access to the brain and opioid receptor sites. It produces a rapid and dose-dependent clinical response which reaches the maximum attainable for this class of drug. However, in the absence of other anaesthetic supplements, the dose of fentanyl required to achieve full analgesia is 25 µg kg^{-1} or higher and the ensuing postoperative respiratory depression reduces the clinical benefit of its intraoperative use (Cooper et al., 1981). Pharmacological control of this respiratory depression which allows adequate postoperative analgesia would extend the intraoperative use of opioid anaesthesia.

Buprenorphine is a partial agonist, also of high lipid solubility and receptor affinity but of a lower intrinsic activity (Dum and Herz, 1981). This and other features of its actions have restricted its application in intraoperative anaesthesia, although as an analgesic for postoperative use its efficacy is well recognized (Harcus, Ward and Smith, 1980; Ellis et al., 1982). Buprenorphine is also slow to reach its full effect, but once established it has a long duration of effect resistant to antagonism with naloxone (Orwin, 1977; Gibbs, Johnson and Davis, 1982).

We have conducted a series of *in vitro* experiments to examine individual and interactive receptor binding properties of these two compounds in an attempt to understand possible receptor mechanisms which may mediate the different clinical effects of these drugs.

SUMMARY

Receptor binding assays were undertaken in an attempt to elucidate the opioid binding characteristics of fentanyl and buprenorphine, and to investigate some of the differences between them. Buprenorphine showed slow receptor association (30 min), but with high affinity to multiple sites from which dissociation was very slow ($T_{½}$ = 166 min) and incomplete (50% binding after 1 h). This contrasted with the receptor binding of fentanyl, which achieved rapid equilibrium (within 10 min) and dissociated equally rapidly ($T_{½}$ = 6.8 min) and completely (100% by 1 h). Competitive displacement showed buprenorphine displacement of fentanyl binding was concentration- and time-dependent over ranges encountered in clinical use, but buprenorphine binding was displaced with only very high concentrations of other opioids. These findings offer pharmacodynamic explanations for the differences in fentanyl and buprenorphine analgesic response profiles and suggest how binding interactions might be applied to therapeutic use.

MATERIALS AND METHODS

Opioid receptor binding assay

Male Wistar rat (250–300 g) forebrain (whole brain minus brainstem and cerebellum) was used as a source of opioid receptors. Rats were decapitated and the tissue rapidly dissected, weighed, placed in 30 volumes of Tris HCl buffer (50 mmol $litre^{-1}$, pH 7.4 at 20 °C), and homogenized with an Ultra-Turrax superspeed homogenizer. The homogenate was resuspended in 30 volumes of Tris buffer, incubated in a shaking water-bath at 37 °C for 30 min, recentrifuged and resuspended in 50 volumes of Tris

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buffer. Ligand binding assays were performed as described previously (Villiger and Taylor, 1981, 1982). Tubes contained 1.0 ml of membrane preparation (20 mg wet weight), 20–100 μlitre [^{3}H]buprenorphine (30 Ci mmol^{-1}; Radiochemical Centre, Amersham) or [^{3}H]fentanyl (12.4 Ci mmol^{-1}; Janssen Pharmaceutica, Beerse, Belgium), 20–100 μlitre drug (where applicable) and Tris buffer to give a final incubation volume of 2.0 ml. Following incubation at 25°C for 30 min, bound was separated from free [^{3}H]opioid by rapid filtration through Whatman GF/B glass fibre filters using a Millipore vacuum manifold. The filters were then removed carefully, dried and placed in vials to which 8.0 ml of a toluene–Triton X-100 scintillation cocktail was added, and radioactivity from labelled opioid was estimated by liquid scintillation spectrometry at a counting efficiency of 28–30%.

Non-specific binding was defined as that occurring in the presence of buprenorphine 1.0 μmol litre^{-1} when [^{3}H]buprenorphine was used, and levorphanol 1.0 μmol litre^{-1} in [^{3}H]fentanyl binding experiments. Except when saturation isotherms were being constructed, [^{3}H]fentanyl and [^{3}H]buprenorphine binding were assayed at 2 and 1 nmol litre^{-1} respectively.

Dissociation kinetics were analysed using computerized non-linear regression analysis (Sedman and Wagner, 1974).

RESULTS

Binding affinities and binding sites

Scatchard analysis of [^{3}H]buprenorphine binding suggests that this drug binds with high affinity (K_D = 1.13 nmol litre^{-1}) to a large, apparently homogenous number of binding sites (34.0 pmol/g tissue wet weight) (fig. 1). In contrast, [^{3}H]fentanyl binding was characterized by curvilinear Scatchard plots suggesting both high (K_D = 0.5 nmol litre^{-1}) and lower (K_D = 4.3 nmol litre^{-1}) affinity binding sites. Also, [^{3}H]fentanyl labelled only 24% (B_{max} = 8.4 pmol g^{-1}) of the sites labelled by [^{3}H]buprenorphine.

Drug binding kinetics

Binding of [^{3}H]fentanyl is characterized by a comparatively rapid association with the receptor, with equilibrium being achieved by 10 min. [^{3}H]Buprenorphine binding was a slower process, taking 30 min to achieve equilibrium (fig. 2).

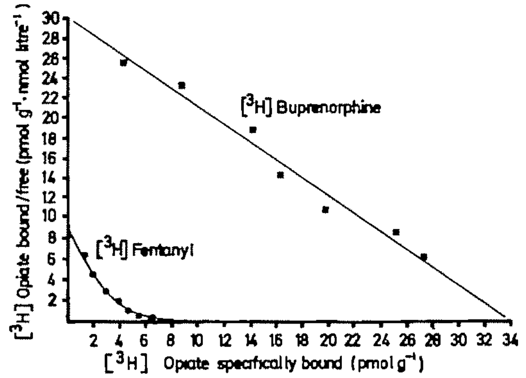

FIG 1. Scatchard plots of [^{3}H]fentanyl and [^{3}H]buprenorphine binding to homogenates of rat forebrain. Scatchard plots were derived from saturation isotherms which were obtained by assaying binding at increasing concentrations of [^{3}H]ligand (0.25–15 nmol litre^{-1} for [^{3}H]fentanyl and 0.1–15 nmol litre^{-1} for [^{3}H]buprenorphine) Values given are the means of four experiments (SD < 15% of the mean at all points).

Dissociation of both tritiated opioids from the receptor was biphasic. Dissociation of [^{3}H]fentanyl was characterized by an initial rapid phase ($T½$ = 0.4 min) followed by a slower phase ($T½$ = 6.8 min), with 100% of the drug dissociated by 60 min. Again, in contrast, dissociation of [^{3}H]buprenorphine was more sluggish, exhibiting fast and slow phases with half-lives of 5.6 and 166.4 min, respectively. Another important difference was that 50% of [^{3}H]buprenorphine remained bound after 60 min.

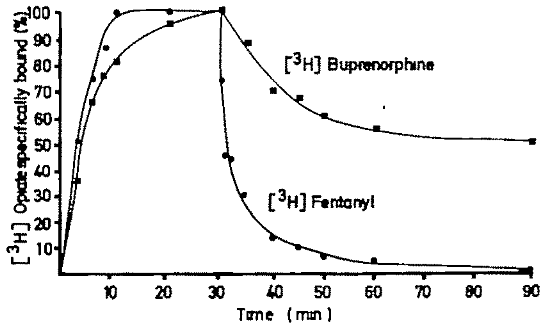

FIG 2. Association and dissociation of [^{3}H]fentanyl and [^{3}H]buprenorphine to and from the opioid receptor. Association rates were established by determining specifically bound drug at times from 0 to 30 min Dissociation rates were determined by adding levorphanol 1 μmol litre^{-1} (for [^{3}H]fentanyl) or buprenorphine 1 μmol litre^{-1} (for [^{3}H]buprenorphine) at 30 min and assaying specific binding at the times indicated. Values given represent the means of three experiments (SD < 15% of the mean at all points).

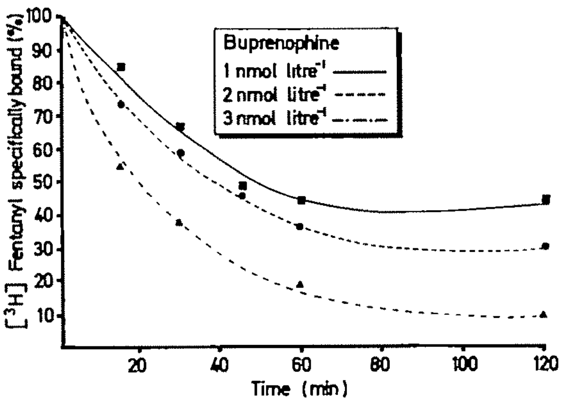

FIG 3. Buprenorphine-induced dissociation of [^{3}H]fentanyl from the opioid receptor [^{3}H]Fentanyl 2 nmol litre^{-1} was equilibrated for 30 min to achieve binding saturation Buprenorphine 1, 2 or 4 nmol litre^{-1} was then added and specific fentanyl binding assayed at times from 0 to 120 min Values given are the mean of four experiments (SD < 15% at all points).

Buprenorphine's action on [^{3}H]fentanyl binding

(a) *Fentanyl displacement by addition of buprenorphine.* After 30 min equilibration, [^{3}H]fentanyl 2 nmol litre^{-1} binding showed a biphasic, dose-dependent dissociation following the addition of buprenorphine 1, 2 or 4 nmol litre^{-1}. Thirty minutes after the introduction of buprenorphine, 67%, 60% and 38% of the fentanyl remained bound for each of the buprenorphine solutions, respectively. At 2 h the amount remaining bound was 48%, 30% and 9% for the same solutions (fig. 3).

(b) *Fentanyl binding after membrane pre-incubation with buprenorphine.* Simultaneous addition of [^{3}H]fentanyl 2 nmol litre^{-1} and buprenorphine 0.5, 1 or 2 nmol litre^{-1} resulted in 65%, 31% and 20% [^{3}H]fentanyl binding in each of the mixtures, respectively. Pre-incubation of membranes for 45 min with the same buprenorphine solutions enhanced significantly the displacement potency of buprenorphine ($P < 0.01$:paired t test) with displacement of 63%, 88% and 97% of [^{3}H]fentanyl from the receptor sites (i.e., only 37%, 12% and 3% of [^{3}H]fentanyl remained bound) (fig. 4).

(c) *Buprenorphine and fentanyl affinities for receptors labelled with [^{3}H]fentanyl.* On the basis of these studies, buprenorphine was two to three times more potent than fentanyl in displacing tritiated fentanyl 2.0 nmol litre^{-1} from μ receptors. The respective molar concentrations giving 50% inhibition of [^{3}H]fentanyl binding were 0.6 ± 0.1 nmol litre^{-1} for buprenorphine and 1.4 ± 0.1 for fentanyl. Calculated on a mass basis, the IC$_{50}$ values for buprenorphine and fentanyl then become 281 pg ml^{-1} and 471 pg ml^{-1}, respectively, giving a potency ratio of 1.7 for buprenorpine to fentanyl.

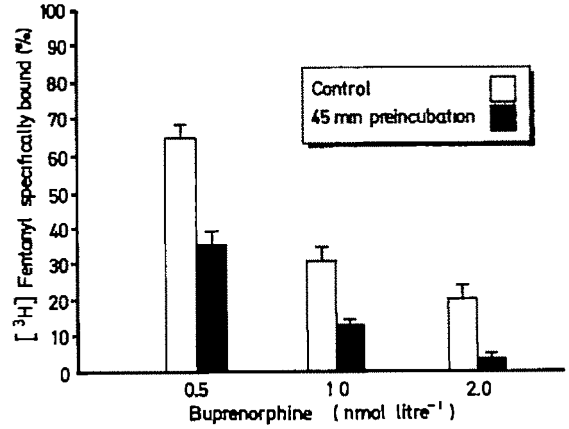

FIG 4 The effect of preincubating membranes with buprenorphine on buprenorphine displacement of [^{3}H]fentanyl 2.0 nmol litre^{-1}. The percent of total [^{3}H]fentanyl specific binding was determined when buprenorphine 0 5, 1.0 or 2 0 nmol litre^{-1} was added 45 min before, or at the same time as, initiation of the reaction with [^{3}H]fentanyl. Specific binding was assayed 30 min after the addition of [^{3}H]fentanyl Values given are the mean ± SD of four experiments

DISCUSSION

The distinction between agonist and agonist–antagonist response profiles is not sufficient to explain many of the clinical features of fentanyl and buprenorphine. Buprenorphine has a high lipid solubility (log of the partition coefficient between heptane and 0.1-M phosphate buffer pH 7.4 = 1.78 (Hambrook and Rance, 1976)), as does fentanyl (log of the partition coefficient between octanol and water at pH 7.4 = 2.98 (Leysen, Gommern and Niemegeers, 1983)), making for ready CNS access, so the slow onset of the action of buprenorphine is attributable probably to pharmacodynamic rather than pharmacokinetic factors. The observed *in vitro* studies showing that it took 10 min to establish drug–receptor equilibrium with fentanyl, compared with 30 min for buprenorphine could explain, in part, their temporal differences in attaining full analgesic efficacy.

Our results indicate also that buprenorphine binds to four times the number of receptors labelled by fentanyl. This is consistent with the idea that fentanyl has selective affinity for morphine (μ) receptors (Villiger, Ray and Taylor, 1983) while buprenorphine is comparatively non-selective, binding to μ, δ (enkephalin) and K (benzomorphan) sites (Villiger and Taylor, 1981; Wood, 1982; Villiger, 1984). Analgesia in clinical situations may be mediated by actions at the high affinity μ_1 sites as proposed by Wolozin and Pasternak (1981). Binding of buprenorphine to other opioid receptors may be less important in generating analgesia, but may bring about the observed antagonistic responses, for example actions on the K receptor being antagonistic to μ receptor effects (Sadee, Rosenbaum and Herz, 1982).

Duration of action for most agents is a function of their plasma concentration, response times reflecting their fate in the body as they are distributed, metabolized or excreted. Fentanyl responses parallel plasma concentration (Stoeckel et al., 1982), but this is not so for buprenorphine, the actions of which (6 h or more (Cowan, Lewis and Macfarlane, 1977)) extend well beyond plasma half-life times of 3–5 h (Bullingham, McQuay and Moore, 1983). Although pharmacokinetic factors could account for this in part, the distinction might be explained further by differences observed with *in vitro* binding. Fentanyl dissociation is both rapid and almost complete, while that for buprenorphine is both very slow and incomplete, 50% of the drug remaining bound 1 h after attempted washout. This sluggish dissociation of buprenorphine from opioid receptors may account for the inability of naloxone to reverse established buprenorphine effects. The IC$_{50}$ for naloxone displacing [^{3}H]buprenorphine is approximately 100 nmol litre^{-1} (Villiger and Taylor, 1981), while only 2.5-nmol litre^{-1} solutions of naloxone are needed to produce 50% inhibition of [^{3}H]fentanyl binding (Villiger, Ray and Taylor, 1983). On this basis, 40 times the dose of naloxone would be needed to reverse comparable concentrations of buprenorphine as opposed to fentanyl receptor binding.

When utilized concurrently, the kinetics of fentanyl dissociation will depend on the dose of buprenorphine introduced and the timing of administration. Based on these *in vitro* studies, concurrent buprenorphine use at a concentration of 4 nmol litre^{-1} (or approx. 2 ng ml^{-1}) will effectively displace 90% of bound fentanyl 2 nmol litre^{-1} or 0.7 ng litre^{-1} within 2 h. If the buprenorphine precedes fentanyl administration, buprenorphine 2.0 nmol litre^{-1} can suppress almost completely any subsequent binding of equimolar concentrations of fentanyl. These values are within the ranges of plasma concentrations associated with the use of these drugs in clinical practice. How plasma concentrations relate to concentrations at opioid receptor sites is not known.

Distinctions in receptor binding may potentially explain several aspects of clinical experience with buprenorphine and fentanyl. In particular, their pharmacodynamic differences in *in vitro* receptor binding offer explanations for temporal differences in onset and duration of action as well as their reversal characteristics with naloxone. Further application in combined sequences may have bearing on the use of buprenorphine for treatment of drug withdrawal effects (Jasinski, 1981) and in the reversal of acute opioid effects, as suggested by De Castro (1979), who proposed buprenorphine as an antagonist to fentanyl anaesthesia.

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COMPARATIVE PHARMACOLOGY OF THE KETAMINE ISOMERS

Studies in Volunteers

P. F. WHITE, J. SCHÜTTLER, A. SHAFER, D. R. STANSKI, Y. HORAI AND A. J. TREVOR

SUMMARY

The clinical and electroencephalographic (EEG) effects of the individual ketamine isomers were compared with the racemic mixture in five volunteers who received each drug on a separate occasion. Racemic ketamine 275 ± 25 mg, S(+) ketamine 140 ± 21 mg or R(−) ketamine 429 ± 37 mg produced an anaesthetic state lasting 6 ± 2 min (mean ± SD). However, the EEG evaluation of the R(−) isomer revealed less overall slowing, and an absence of the large slow wave complexes produced by the S(+) isomer and the racemic mixture. The pharmacokinetic profiles for the individual isomers of ketamine did not differ significantly from the racemic mixture. Even though the apparent anaesthetic state produced in these healthy volunteers did not differ qualitatively between the three drug groups, recovery times (assessed using a standardized battery of psychometric tests) were consistently shorter following the individual isomers compared with the racemic mixture. The serum ketamine concentrations associated with regaining consciousness and orientation were consistent with an S(+):R(−) isomer potency ratio of 4:1. In terms of their ability to impair psychomotor function, the S(+):R(−) potency ratio varied from 3:1 to 5:1. After comparable degrees of CNS depression, we conclude that the more potent S(+) isomer of ketamine was associated with a more rapid recovery of psychomotor skills than the currently used racemic mixture.

Preliminary clinical studies with the ketamine isomers suggested that there were quantitative and qualitative differences between the enantiomers in their effects on the central nervous system (White et al., 1980). We reported differences between the optical isomers of ketamine in terms of their anaesthetic potency, intraoperative effects, postoperative analgesia and side-effects in surgical patients. Based on this earlier study, the more potent S(+) isomer appeared to offer significant clinical advantages over R(−) ketamine.

Since racemic mixtures (of stereoisomers) do not necessarily behave as compounds containing equal proportions of the individual isomers (Haley and Gidley, 1970), further studies were needed to assess the potential advantages of S(+) ketamine compared with the currently available racemate (Ketalar, Ketaject). The present investigation was designed to evaluate the pharmacokinetic characteristics and pharmacodynamic effects of the optical isomers (*v.* racemic ketamine) in volunteers receiving the drugs in a controlled, cross-over fashion. The comparative effects of these drugs on the central nervous system (CNS) were assessed using clinical signs, the electroencephalogram (EEG), and a battery of psychometric tests. Finally, relationships between the serum concentrations of the three drugs and recovery times were used to assess their relative potencies.

SUBJECTS AND METHODS

Five healthy, male volunteers (age 36 ± 3 yr, weight 75 ± 3 kg (mean ± SD)) received racemic ketamine or one of the two F.D.A. Investigative New Drugs No. 14107, S(+) ketamine, or R(−) ketamine, by infusion i.v. at 7–14 day intervals using a cross-over experimental programme. Each

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volunteer received all three drugs on separate occasions. Two volunteers received S(+) ketamine, followed by racemic ketamine, and then the R(−) isomer. The remaining three volunteers received R(−) ketamine, followed by racemic ketamine, and finally, the S(+) isomer. The study was approved by the local Committee on Human Research, and informed consent was obtained from each subject.

Resolution of the two enantiomers followed a procedure involving recrystallization of the (+) or (−)-tartaric acid salts (Meliska, Greenberg and Trevor, 1980). On treatment of (−) ketamine-free base with hydrochloric acid, the S(+) ketamine hydrochloride salt was formed with m.p. 258–261 °C and $[\alpha]_D^{25} = +93.6$ °C ($c = 2.0$, water). On treatment of free base (+) ketamine with acid, R(−) ketamine hydrochloride was formed with m.p. of 256–258 °C and $[\alpha]_D^{25} = -93.5$ °C ($c = 2.0$, water). These separation procedures resulted in resolution exceeding 90% for each isomer. The two isomers were administered as the hydrochloride salt and all designations of sign of optical rotation refer to the respective salt forms.

A standard battery of psychomotor tests was administered on the evening before each study. The battery of tests included the time distortion index (Yesavage, Freeman and Bourgeois, 1978), Trieger test (Newman, Trieger and Miller, 1969), five separate visual analogue scales (Bond and Lader, 1974), and symbol–digit test (Lezak, 1967). On the morning of each study, the volunteers were taken to the recovery area where two peripheral catheters were inserted i.v. under local anaesthesia (one for drug and fluid administration and the other for obtaining the blood samples required for drug analysis). An electrocardiogram (four-lead EEG), electro-oculogram (eye movement), and Dinamap (Model 845) arterial pressure monitor were applied. Supplementary oxygen was provided throughout the study period using nasal cannulae. Predrug "baseline" psychometric test scores were obtained. Glycopyrrolate 0.2 mg i.v., an antisialagogue without CNS effects, was administered. Subsequently, racemic ketamine 50 mg min^{-1}, S(+) ketamine 25 mg min^{-1}, or R(−) ketamine 75 mg min^{-1} was administered over a 5–7-min interval by continuous infusion i.v. using an Autosyringe (Model 5A) pump. The infusion was discontinued after 5 min (or when *no* further changes were observed in the EEG over a 30–60-s interval).) The infusion rates were based on results from previous studies with the ketamine isomers (Ryder, Way and Trevor, 1978; White et al., 1980). The total doses of racemic ketamine, S(+) ketamine, and R(−) ketamine were 275 ± 25 mg, 140 ± 21 mg, and 429 ± 37 mg, respectively (mean ± SD).

A clinical assessment was performed at 1-min intervals during and immediately after the drug infusion and included: (1) responsiveness to verbal commands, (2) the presence or absence of the eyelid reflex, and (3) the degree of spontaneous motor activity, facial grimacing and vocalizations on a scale from 0 (none) to 3 (severe). After termination of the infusion, the times to regaining the eyelid reflex, responsiveness to simple commands (e.g. "open your eyes", "squeeze my hand"), and orientation to person, place and time were recorded. The duration of anaesthesia (min) was defined as the duration of loss of the eyelid reflex. The battery of psychomotor tests was repeated when the subject was fully-oriented and, subsequently, at 15-min intervals until the test scores returned to the predrug baseline values (±10%). Amnesia was assessed at the time the subject was judged to be fully oriented (George and Dundee, 1977). A follow-up questionnaire was completed within 24 h of each study to assess the relative incidences of side-effects (e.g. dreaming, dizziness).

The time distortion index relates to the subject's ability to estimate 30 s (the actual elapsed time was recorded). Trieger tests were scored in terms of the number of dots missed (maximum 40) and the total distance from the missed dots to the nearest line (maximum 200 mm). Each individual visual analogue scale was scored from 0 (almost asleep, tired, clumsy, fuzzy or drowsy) to 100 mm (wide awake, energetic, well-coordinated, clear-headed or alert). The symbol–digit test (matching a series of symbols and numbers) was scored in terms of the number of correct responses and number of attempted matches. The symbol–digit matching key was changed before each test. Temporal changes in the psychometric tests were evaluated using repeated measures of analysis of variance and the average time required to return to the predrug baseline (± 10%) was reported. Continuous variables were analysed using Statistical Analysis System (SAS) (SAS Institute, Inc., SAS Circle, P.O. Box 8000, Cary, North Carolina 27511) one-way analysis of variance and Duncan's multiple range test ($P < 0.05$). Categorical variables were evaluated with Chi-square analysis ($P < 0.05$).

Samples of venous blood were obtained at 1-min intervals during the infusion and, subsequently, at 5–60-min intervals for 480 min. Specimens were assayed for total ketamine and its principal metabolite (norketamine) using a modified version of the gas chromatographic procedure of Chang and Glazko (1972) as described previously (White, Johnston and Pudwill, 1975). Serum concentration *v.* time data for each volunteer were fitted to an open two-compartment model using extended least squares nonlinear regression analysis (L. Sheiner, unpublished report). Pharmacokinetic parameters were derived using standard formulae (Gibaldi and Perrier, 1975).

RESULTS

All three drugs produced an anaesthetic state (absence of eyelid reflex) 3 ± 1 min after starting the infusion and lasting 6 ± 2 min (mean ± SD). However, the individual ketamine isomers produced differing effects on the EEG. When S(+) ketamine or the racemic mixture were infused to produce a state of clinical anaesthesia, a progressive decrease in EEG amplitude and frequency occurred, followed by intermittent high amplitude polymorphic delta activity (figs 1 and 2). In contrast, R(−) ketamine was unable to suppress the EEG activity to the same extent even though larger doses of the (−) isomer were infused (fig. 2). Both isomers and the racemate were infused until plateau effects were observed with respect to changes in the EEG (maximal slowing).

The magnitude and duration of spontaneous motor (or myoclonic) activity, facial grimacing or vocalization during the infusions did not differ between the three treatment groups. In addition, haemodynamic changes during the infusions did not differ significantly between the three groups (fig. 3). Maximal increases (above baseline values) in mean arterial pressure and heart rate were 42–59% and 56–84%, respectively. There were *no* correlations between changes in arterial pressure or heart rate and the concentrations of ketamine or norketamine.

Pharmacokinetic parameters indicated a high clearance and a moderately large volume of distribution for racemic ketamine and its individual isomers (table I). Although there were no significant pharmacokinetic differences between the three drugs, the coefficient of variation for distribution phase kinetic parameters (initial volume of distribution, distribution half-life) ranged from 38% to 78%. In contrast, the coefficients of variation for elimination phase variables were less than 30%. Serum concentrations of ketamine after termination of the racemic ketamine, S(+) ketamine, or R(−) ketamine infusions are summarized in figure 4. The serum concentrations associated with regaining consciousness and orientation are summarized in table II. The ratios of these serum concentrations were consistent with a S(+):R(−) isomer potency ratio of 4:1. Recovery times were decreased following the individual isomers compared with the racemic mixture (table II). Results of the psychometric testing were also consistent with a more rapid recovery after the individual isomers, irrespective of the sequence of drug administration (table III). In terms of their ability to impair psychomotor functioning, the S(+):R(−)

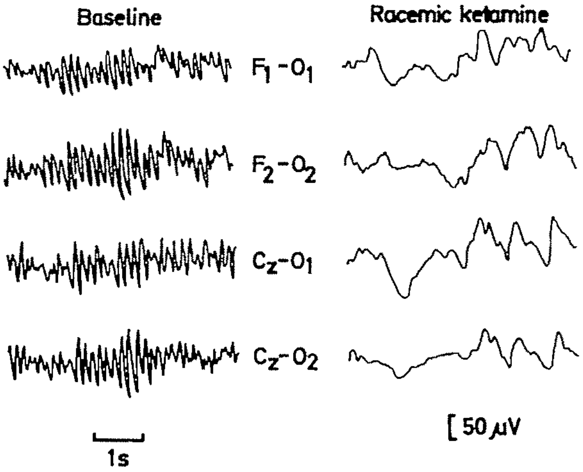

FIG 1. The control (baseline) four-lead EEG in an awake volunteer and the maximal slowing recorded immediately after an infusion of racemic ketamine I.V.

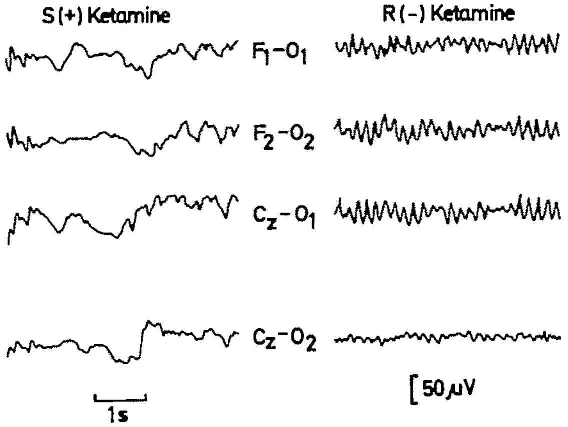

FIG 2. A typical four-lead EEG pattern demonstrating the *maximal* slowing during or immediately after the infusion of S(+) ketamine or the R(−) isomer I.V.

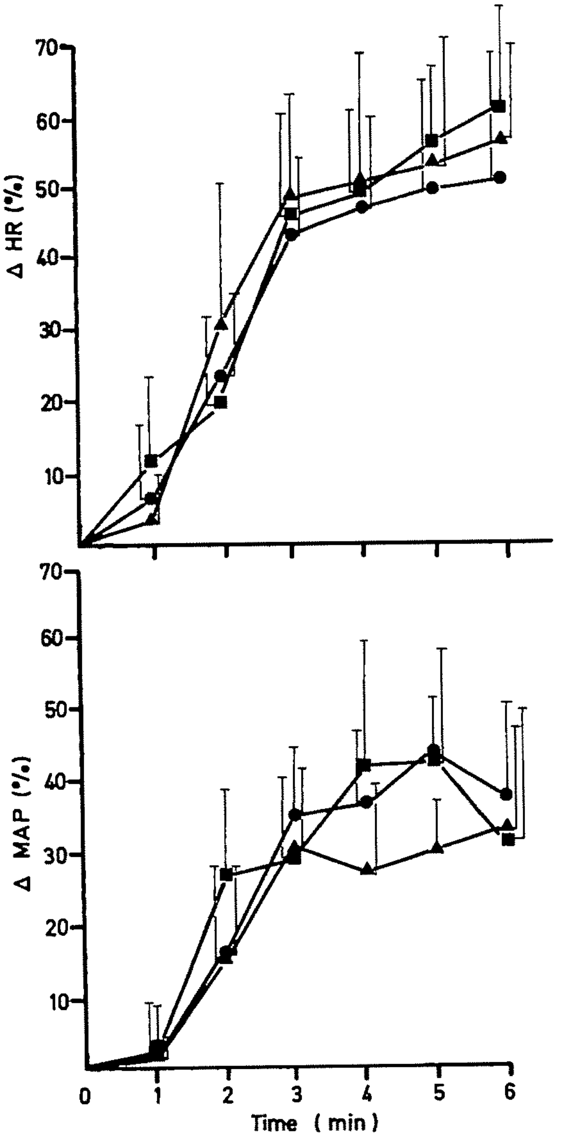

FIG 3. Percentage changes from predrug baseline values in mean arterial pressure (Δ MAP) and heart rate (Δ HR) during the infusion of racemic ketamine (●——●), S(+) (■——■), or R(−) ketamine (▲——▲).

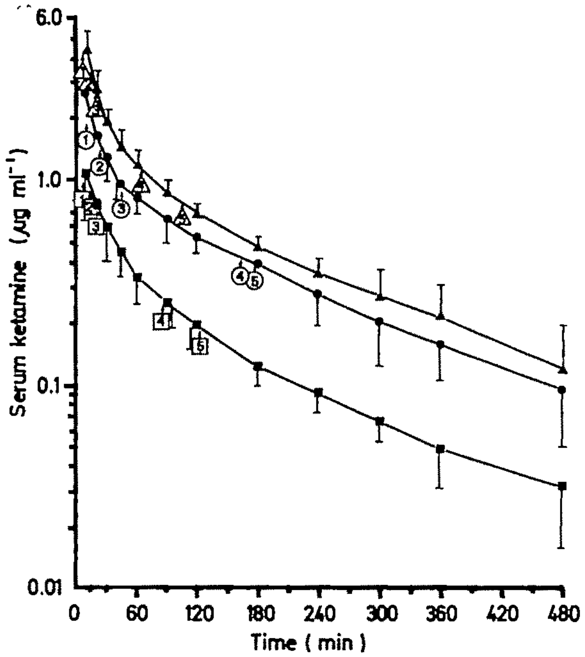

FIG 4. Venous serum concentrations of ketamine (mean values ± SD) on a logarithmic scale as a function of time after infusion of racemic ketamine (●——●), S(+) ketamine (■——■) or R(−) ketamine (▲——▲). Arrows indicate time of awakening, for example, opened eyes (1); ability to follow simple command, for example, squeezed hand (2); orientation to person, place and time (3); and return to predrug scores for Trieger (4) and symbol–digit (5) tests.

potency ratio varied from 3:1 to 5:1.

The incidence of dreaming did not differ between the drug groups. In general, the dreams were described as pleasant illusionary-type experiences. Amnesia was not associated with either the racemic mixture or the individual isomers. Incidences of postanaesthetic side-effects (dizziness 47%, floating sensation 67%, diplopia 60%) did not differ between the three groups.

DISCUSSION

The sequential changes in the EEG produced by racemic ketamine and the S(+) isomer were similar to the EEG pattern reported previously by Domino,

TABLE I. *Pharmacokinetic parameters following administration of racemic ketamine or one of its individual isomers (mean values ± SD)*

Drug group	Distribution half-life (min)	Elimination half-life (min)	Clearance (ml kg⁻¹ min⁻¹)	Volumes of distribution Vc (litre kg⁻¹)	 Vd area (litre kg⁻¹)
Racemic ketamine	12.6 ± 8.6	132 ± 32	16.1 ± 4.6	1.0 ± 0.4	2.9 ± 0.5
S(+) ketamine	22.8 ± 14.7	158 ± 45	21.3 ± 1.6	1.6 ± 0.7	4.7 ± 1.1
R(−) ketamine	11.8 ± 9.2	155 ± 42	17.4 ± 2.5	0.9 ± 0.7	3.9 ± 1.3

TABLE II *Time to awakening and orientation (min) and the associated serum concentrations of ketamine ($\mu g\ ml^{-1}$) following infusion of racemic ketamine or one of its individual isomers (mean values ± SD) *Value significantly different from racemic:* $P < 0.05$

	Racemic ketamine		S(+) ketamine		R(–) ketamine	
Variable	(min)	($\mu g\ ml^{-1}$)	(min)	($\mu g\ ml^{-1}$)	(min)	($\mu g\ ml^{-1}$)
Opened eyes	11 ± 3	2.6 ± 0.7	8 ± 1	1.2 ± 0.3*	7 ± 2	5.2 ± 0.8*
Squeezed hand	22 ± 8	1.6 ± 0.5	12 ± 3	1.0 ± 0.3	9 ± 2*	4.1 ± 0.9*
Oriented to person	33 ± 11	1.2 ± 0.3	14 ± 2*	0.9 ± 0.2	10 ± 2*	3.9 ± 0.8*
Oriented to person, place and time	45 ± 10	1.0 ± 0.1	21 ± 2*	0.7 ± 0.2*	18 ± 3*	2.7 ± 0.5*

Chodoff and Corssen (1965). However, the present volunteer study has demonstrated qualitative morphological differences in the EEG patterns produced by the individual ketamine enantiomers (fig. 2). Although dose–response data regarding the ketamine isomers are not available, analyses of the individual EEG tracings using the median frequency demonstrated that a "plateau" effect (maximal slowing) had been reached with each isomer as well as with the racemic mixture (Schüttler, Stanski, White and Trevor; in preparation). Furthermore, there was a correlation between changes in the median frequency and the serum concentrations of ketamine.

The R(−) isomer was unable to achieve the degree of EEG slowing recorded during the infusions of the S(+) isomer or the racemic mixture. This observation is consistent with the reduced hypnotic and analgesic potency of the R(−) isomer (*v.* S(+) isomer) reported in our previous study (White et al., 1980). If the serum concentrations of ketamine associated with specific clinical endpoints (e.g. awakening, orientation) are compared, S(+) ketamine would appear to be approximately four times more potent than the R(−) isomer (tables II and III, fig. 4).

In our earlier clinical study, a significantly higher percentage of patients receiving R(−) ketamine required supplementary anaesthetic drugs to complete the surgical procedure, compared with those receiving the S(+) isomer of ketamine. The inability of R(−) ketamine to produce an adequate depth of anaesthesia in the presence of surgical stimulation might explain the higher incidence of intraoperative complications such as movement and tachycardia, and greater need for adjunctive drugs. Furthermore, we would postulate that these clinical differences may be related in part to the differing analgesic potencies of the individual isomers (Ryder, Way and Trevor, 1978). If the S(+) isomer is a more effective analgesic, this might also contribute to the lower incidence of emergence delirium observed in the early postoperative period in the prior clinical study. We would speculate that pain increases anxiety as well as the incidences of postanaesthetic emergence phenomena.

Anaesthetic recovery following an i.v. infusion of either racemic ketamine or one of its optical isomers was assessed using clinical signs and a battery of psychomotor tests. These tests were consistent with a more rapid rate of recovery following either of the isomers compared with the currently used racemic mixture (tables II and III). One might speculate that the more rapid recovery following the R(−) isomer was a result of its more limited depressant effects on the CNS. Yet, how does one explain a slower recov-

TABLE III. *Time required for psychomotor scores to return to predrug baseline score (min) and the associated serum ketamine concentrations ($\mu g\ ml^{-1}$) following infusion of racemic ketamine or one of its individual isomers (mean values ± SD) *Value significantly different from racemic:* $P < 0.05$

	Racemic ketamine		S(+) ketamine		R(–) ketamine	
Test	(min)	($\mu g\ ml^{-1}$)	(min)	($\mu g\ ml^{-1}$)	(min)	($\mu g\ ml^{-1}$)
Analogue scales	161 ± 21	0.4 ± 0.1	150 ± 22	0.2 ± 0.03*	123 ± 19	0.7 ± 0.2*
Trieger test	164 ± 17	0.4 ± 0.1	87 ± 13*	0.3 ± 0.1*	65 ± 9*	1.1 ± 0.3*
Symbol – digit	178 ± 19	0.4 ± 0.1	122 ± 29	0.2 ± 0.1*	104 ± 19*	0.8 ± 0.3*
Time distortion	118 ± 24	0.5 ± 0.2	74 ± 12*	0.3 ± 0.1	57 ± 20*	1.2 ± 0.8

ery following the racemic mixture compared with S(+) ketamine? The two most plausible explanations are, first, that a greater depth of anaesthesia was achieved with the racemic mixture (*v*. S(+) ketamine) or, second, that the presence of the less potent R(−) isomer in the racemic mixture exerted an inhibitory effect on the rate of recovery from S(+) ketamine. The fact that the EEG patterns achieved with the racemic mixture and the S(+) isomer were virtually identical would argue against the first explanation. However, it is possible that the EEG is simply not a good index of anaesthetic depth.

Regarding the second possibility, the pharmacokinetic profiles for the S(+) isomer and the racemic mixture appear to be similar (table I). However, the gas chromatographic method used to measure serum ketamine concentrations does not permit assessment of the actual concentrations of the *individual* isomers in the serum following administration of *racemic* ketamine. It is possible that the measured concentrations following racemic ketamine do not reflect a constant 50:50 distribution of the individual isomers. In fact, chiral interactions in which metabolism of one enantiomer of a drug is inhibited by its optical antipode have been reported for the isomers of the analgesic propoxyphene (Murphy et al., 1976) and the psychotomimetic amine 1-(2, 5-dimethoxy-4-methylphenyl)-2-aminopropane (McGraw, Callery and Castagnoli, 1977). Thus, inhibition of metabolism of the more potent enantiomer, S(+) ketamine, by the R(−) isomer could account for the prolongation of recovery observed following racemic ketamine.

When psychometric tests are administered repeatedly, a certain degree of improvement (so-called learning behaviour) would be expected; however, a plateau of performance is usually attained after two to four repetitions (Jenson and Rohwer, 1966). In our volunteers, the baseline scores before the initial drug exposure were not significantly diffferent from those measured before the third infusion. Furthermore, since this learning phenomenon would be expected to occur irrespective of the drug administered, it could not explain the differing recovery rates for the two optical isomers (*v*. the racemic mixture). Alternatively, it might be suggested that the development of "acute" tolerance (Cumming, 1976), or tolerance which develops after only a single prior exposure to the drug (Meliska and Trevor, 1978) could explain the more rapid recovery times for the individual enantiomers of ketamine. However, the fact that the relative recovery times following racemic ketamine (or either one of its isomers) were similar *irrespective* of the sequence of drug administration, would argue against tolerance as an explanation of our findings.

In summary, R(−) ketamine was unable to produce the same degree of EEG slowing as S(+) ketamine and, therefore, one would predict that it would be more difficult to achieve an adequate depth of anaesthesia with the less potent R(−) isomer. The more potent S(+) isomer, on the other hand, was able to achieve the same degree of EEG slowing produced by racemic ketamine. Furthermore, after comparable degrees of CNS depression, a more rapid recovery of psychomotor skills was noted with the S(+) isomer than the racemic mixture. We conclude that the more potent S(+) isomer of ketamine would offer clinically useful advantages over the currently used racemic mixture.

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EFFECT OF A MIXTURE OF PYRIDOSTIGMINE AND ATROPINE ON FORCED EXPIRATORY VOLUME (FEV_1), AND SERUM CHOLINESTERASE ACTIVITY IN NORMAL SUBJECTS

B. F. FELDT-RASMUSSEN, K. GEFKE, H. MOSBECH AND H. K. HANEL

SUMMARY

Pyridostigmine 0.143 mg kg^{-1} (maximum 10 mg) and atropine 0.0143 mg kg^{-1} (maximum 1 mg) were administered i.v. to six healthy male volunteers. Peripheral venous blood samples were drawn for measurement of serum cholinesterase activity. Maximum inhibition of the enzyme was found 5 min after injection with a decrease to 27 ± 5% (mean ± SEM) of the original activity. Forced expiratory volume in the first 1s (FEV_1) was measured at fixed time intervals for 90 min. No decrease in FEV_1 was observed; on the contrary, there was a small increase. We conclude that atropine effecively antagonizes the muscarinic side-effects of pyridostigmine on bronchial smooth muscle tone and bronchial secretions, when administered in clinical doses to normal human subjects.

Inhibition of acetylcholinesterase (A-ChE) activity by cholinesterase (ChE) inhibitors is used clinically to reverse the effects of non-depolarizing neuromuscular blocking drugs. Certain muscarinic side-effects such as bradycardia are antagonized by atropine administered either simultaneously (Baraka et al., 1981) or before the ChE inhibitor (Katz, 1967). However, when these reversal agents are administered at the end of surgery, just before extubation of the trachea, bronchial constriction and increases in bronchial secretions are muscarinic side-effects of particular importance. At this time other drugs which can influence bronchomotor tone will have been given, and it will be difficult to distinguish between the specific actions of the individual drugs. The present study was designed to investigate whether the muscarinic side-effects in the lung are fully antagonized when a combination of pyridostigmine and atropine is administered i.v. in clinical doses to normal subjects receiving no other medication before or during the study.

SUBJECTS AND METHODS

The study was performed in six healthy male volunteers (28–34 yr) with no previous history of asthma. All gave informed consent. The procedure was approved by the Regional Ethics Committee.

Each subject received pyridostigmine 0.143 mg kg^{-1} (maximum 10 mg) mixed with atropine 0.0143 mg kg^{-1} (maximum 1 mg) i.v. over 1 min. Forced expiratory volume in the first 1 s (FEV_1) was used to evaluate bronchial constriction. The test was carried out with the subjects in the upright position blowing as hard as possible through an electronic spirometer (Spiritron, Dräger AG). Measurements were obtained before the injection of the pyridostigmine–atropine mixture, and at fixed time intervals for 90 min following administration. To ensure that the FEV_1 value resulted from a maximum blowing effort, this was repeated on three occasions and only the highest value accepted. Serum cholinesterase (S-ChE) activity (E.C.3.1.1.8) was measured in blood samples drawn at specified time intervals from the antecubital vein of the arm opposite to that used for administration of the anti-ChE drug. The method of Kalow and Genest (1957) was used to determine S-ChE activity. The dibucaine number was measured for characterization of the phenotype of S-ChE (Kalow and Genest, 1957). The normal range in our laboratory for S-ChE activity ($n = 453$) was: 680–1560 u. $litre^{-1}$ (Viby-Mogensen and Hanel, 1977), with a coefficient of variation

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of 0.015–0.020. All persons tested had normal S-ChE activity and a normal dibucaine number.

During the study the ECG and arterial pressure were monitored continuously. Statistical evaluation was performed using a polynomial regression analysis.

RESULTS

The changes in S-ChE activity with time are shown in figure 1. The S-ChE activity before injection of pyridostigmine was within normal limits. The maximum depression of S-ChE activity occurred 5 min after injection, the activity decreasing to 27 ± 5% (mean ± SEM) of the initial value. Serum ChE activity returned to 50% of its initial activity after 18 ± 4 min (table I). The mean changes in FEV_1 with time after treatment calculated as percent of initial value are presented in figure 2. During the first part of the test period, which coincided with the maximal depression of S-ChE activity, no significant change in FEV_1 was observed. At the end of the observation period a small but significant ($P < 0.05$) increase in FEV_1 was registered.

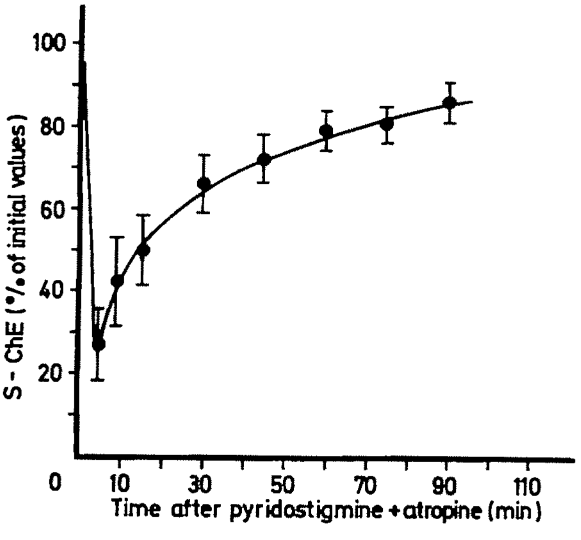

FIG 1. Serum cholinesterase (S-ChE) activity calculated as per-cent of initial values (mean ± SEM) after the administration of pyridostigmine–atropine i.v. mixture to six healthy male volunteers.

The heart rate increased within 2 min in all subjects from the initial measurement of 77 ± 4.2 beat min^{-1} to a maximum mean of 101 ± 10.4 beat min^{-1}.

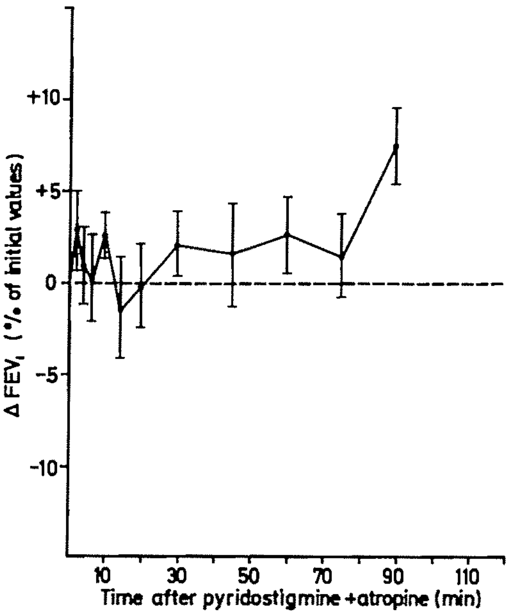

FIG. 2. Forced expiratory volume in the first 1 s calculated as percent of initial values (mean ± SEM) after the administration of pyridostigmine–atropine mixture i.v. to six healthy male volunteers.

During the first 25 min after injection, all of the subjects felt some minor discomfort, characterized by generalized muscle twitches, dysfunction of the tongue and swallowing reflex, and paralysis of accommodation of varying degrees. These symptoms disappeared totally before the end of the test period.

DISCUSSION

The clinical use of ChE inhibitors may be limited because of undesirable muscarinic side-effects. It is known that the muscarinic side-effects on the heart can be prevented by the simultaneous administration of atropine (Kemp and Morton, 1962; Baraka, 1968; Kjellberg and Tammisto, 1970; and Rosner, Kepes and Foldes, 1971). However, the muscarinic side-effects on oropharyngeal secretions and bowel peristalsis are not totally abolished when the anticholinesterase–atropine mixture is used, and this may be important following gastrointestinal surgery (Hannington-Kiff, 1969). Similarly, if anticholinergic muscarinic side-effects causing bronchoconstriction were to persist despite the use of atropine, this would be of significance in patients with pre-existing lung disease. No previous reports have examined bronchial function in patients treated with an anticholinesterase–atropine combination such as is used in clinical practice.

In the present study, S-ChE activity was measured. The ultimate measure of motor endplate ChE can be obtained only from muscle biopsies and is

TABLE I. *Serum cholinesterase (S-ChE) activity following pyridostigmine–atropine administration in six healthy male volunteers*

No.	Age (yr)	Wt (kg)	Ht (cm)	Serum cholinesterase activity: Before pyridostigmine–atropine (u. litre^{-1})	Serum cholinesterase activity: Per cent of initial values at max. inhib.	Time to I_{50} (min)
1	28	77	187	1150	67 after 5 min	Not inhib. to I_{50}
2	30	62	178	710	25 after 5 min	15
3	33	73	178	830	26 after 5 min	25
4	30	88	183	1270	17 after 5 min	28
5	30	73	174	1250	8 after 5 min	17
6	34	81	189	935	17 after 5 min	25
Mean	31	76	182	1024	27 after 5 min	18
SEM	± 0.82	± 3 7	± 2.5	± 10	± 9	± 4

therefore rarely, if ever, measured clinically. S-ChE activity was measured to enable us to compare our results with those from previous reports using different ChE inhibitors. It is known that ChE inhibitors will effect their pharmacological activity in any tissue containing ChE and that there is a parallelism between the therapeutic efficacy and the inhibitory effect of pyridostigmine on circulating ChE (Grob, Garlick and Harvey, 1950; Foldes and Smith, 1966). Furthermore, pyridostigmine is a more potent inhibitor of motor endplate ChE activity than of S-ChE. Therefore, our measures of S-ChE activity represent an underestimation of the changes in muscle endplate A-ChE—the pharmacologically active agent in neurotransmission (Namba et al., 1980).

Pyridostigmine was used in a dose of 0.143 mg kg^{-1}. This was found to depress S-ChE activity by 73 ± 7%, and is comparable to the results reported by Baraka and colleagues (1981). They found that S-ChE activity was depressed by 70 ± 2% by pyridostigmine 0.25 mg kg^{-1}; neostigmine 0.05 mg kg^{-1} depressed S-ChE activity by 63 ± 7% (pyridostigmine 10 mg is equipotent to neostigmine 2.5 mg as an antagonist of tubocurarine). Serum-ChE in subject number 1 was only reduced to 67% of the initial value. However, the subjective minor discomforts, and the initial increase in heart rate in this individual were similar to those observed in the other subjects. The discrepancy must reflect physiological differences in sensitivity to the drug.

FEV_1 measurements are widely used to evaluate the effect on airway resistance of other pharmacological agents. It is an accepted determinant of bronchial obstruction following bronchial challenge (Cropp et al., 1980). The initial fluctuations in FEV_1 were not significant from a clinical or a statistical point of view. Furthermore, the maximal reduction in FEV_1, of −1.6% of initial values, occurred 9 min after maximal depression of S-ChE was observed. Although no significant decrease in FEV_1 was observed, there was a small but significant increase by the end of the study period. These findings indicate that pre-existing vagal tone is not increased, but rather decreased by the simultaneous administration of the pyridostigmine–atropine mixture.

Atropine, therefore, appears to be an effective antagonist of the possible muscarinic bronchoconstrictor effects of pyridostigmine in non-asthmatic individuals. In asthmatic patients the bronchi may have a lower threshold for vagal stimulation (Gold, 1975; Miller, Fish and Patterson, 1977), but atropine has been demonstrated to protect these patients from allergen-induced bronchospasm (Yu, Galant and Gold, 1972). Whether atropine can also effectively antagonize the possible muscarinic bronchoconstrictor effects of pyridostigmine in asthmatics remains to be documented.

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EFFECTS OF INCREASING DEPTH OF ANAESTHESIA ON PHRENIC NERVE AND HYPOGLOSSAL NERVE ACTIVITY DURING THE SWALLOWING REFLEX IN CATS

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SUMMARY

The effects of increasing depths of anaesthesia on phrenic nerve (PN) activity and hypoglossal nerve (HN) activity during the swallowing reflex elicited by stimulation of the superior laryngeal nerve (SLN) were investigated in 10 cats. Swallowing induced by SLN stimulation always coincided with a characteristic brief burst of PN activity and a large amplitude burst of HN activity. These characteristic responses of PN and HN activities were not influenced by either bilateral vagotomy or neuromuscular blockade, indicating that the characteristic responses of PN and HN activities can be used as indicators of the swallowing reflex in vagotomized and paralysed animals. The results obtained in such animals showed that increasing depth of anaesthesia depressed progressively the swallowing reflex. Detailed analysis of HN activity revealed also that SLN stimulation elicited three different responses of HN activity which had different sensitivities to anaesthesia. However, the characteristic response observed during the swallowing reflex was the most sensitive to increasing depth of anaesthesia.

The swallowing reflex is one of the most important of the reflexes which prevent the entrance of foreign material into the respiratory tract. Although it is an accepted clinical observation that reflex swallowing is frequently lost in anaesthetized patients, the mechanisms by which anaesthesia depresses the swallowing reflex have not been examined systematically.

In experimental animals, reflex swallowing can be elicited readily by electrical stimulation of the superior laryngeal nerve (SLN) and, thus, swallowing is accessible to neurophysiological analysis (Doty, 1951). The act of swallowing requires the integrated action of several cranial motor nuclei among which the hypoglossal nucleus is probably the most important nucleus involved in the buccopharyngeal stage of swallowing (Miller, 1982). The effects of anaesthesia on the behaviour of hypoglossal motoneurones during reflex swallowing are almost unknown, except for a brief description by Sumi (1969). In the present study, we investigated the effects of increasing depth of anaesthesia on hypoglossal nerve (HN) and phrenic nerve (PN) activity during reflex swallowing induced by stimulation of the superior laryngeal nerve.

MATERIALS AND METHODS

Experiments were performed on 10 adult cats weighing 2.8–4.4 kg. The animals were anaesthetized initially with 2–3% halothane in oxygen. The surgical procedure was similar to that described previously (Nishino et al., 1984), and is described briefly. The animals were prepared with tracheal, arterial and venous cannulae, and rectal temperature was maintained close to 38 °C. Both HN and PN were isolated and prepared for recordings of their discharges. The buccopharyngeal stage of the act of swallowing was monitored using an intrapharyngeal balloon catheter connected to a pressure transducer. The internal branch of the right SLN was identified and sectioned near its entrance to the larynx, and the central end was placed on bipolar platinum electrodes in a warm paraffin pool. After the surgical preparation, halothane was discontinued and was replaced by α-chloralose 25 mg kg^{-1} i.v.

The actual investigation was started at least 40 min after the discontinuation of halothane while

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the animal was breathing spontaneously. Breathing was monitored with a pneumotachograph and the tidal volume was obtained by electrical integration of the inspired air-flow signal. End-tidal carbon dioxide concentration was monitored continuously with an infra-red carbon dioxide analyser.

To elicit the swallowing reflex, rectangular wave stimuli of 0.06–0.1 V, 0.5 ms pulse duration at a frequency of 33 Hz were delivered to the SLN as stimulus trains. The strength of the stimulus was varied from animal to animal, but it was approximately three times the minimum voltage necessary to produce prolonged apnoea during 100% oxygen breathing, and was not changed throughout the experiment. Stimulation of SLN was induced during an expiratory period and was maintained for 30 s. This procedure was performed at least five times for each animal. Then, all animals were subjected to bilateral vagotomy and the procedure of SLN stimulation repeated.

After the above procedures in spontaneously breathing animals, pancuronium bromide 0.2 mg kg^{-1} was administered i.v., and the lungs ventilated artificially at a fixed rate and volume (rate × volume = 20 × 50 ml). The end-tidal carbon dioxide concentration was maintained around 4–4.6 kPa by adding a small amount of carbon dioxide to the inspired gas mixture.

To study the effects of increasing depth of anaesthesia, the depth of anaesthesia was varied by administering various concentrations of nitrous oxide (30, 50 and 70%). Each concentration was maintained for 10 min and at appropriate times the procedure of SLN stimulation was repeated. In addition, in these animals the thresholds of the stimulus intensity for the swallowing reflex at each depth of anaesthesia were determined precisely by increasing the stimulus intensity from 0 to 6.0 V in step increments of 0.02 V.

Statistical analysis was performed using Student's *t* test when appropriate.

RESULTS

Characteristics of PN and HN responses during reflex swallowing

Figure 1 depicts the changes in respiration and pharyngeal pressure during SLN stimulation, observed in all animals and reproducible in most of the animals. With the start of SLN stimulation, rhythmic respiration was lost and apnoea ensued. During continuing stimulation of the SLN, the apnoea was broken with brief and small inspiratory movements which accompanied the swallowing acts—identified by the pharyngeal pressure peak and the visual observation of laryngeal movements. The act of swallowing always coincided with a brief burst of PN activity and a large amplitude burst of HN activity which lasted for longer than 300 ms. Various forms of phasic bursts and tonic discharges in HN were also observed during stimulation. Although these discharges were related to non-swallowing movements of the larynx and the pharynx, none of these discharges was associated with swallowing.

The characteristic bursts of PN and HN during swallowing were observed consistently after bilateral vagotomy, and neuromuscular blockade induced by the i.v. administration of pancuronium did not produce any change in the responses of either PN or HN activities (fig. 2).

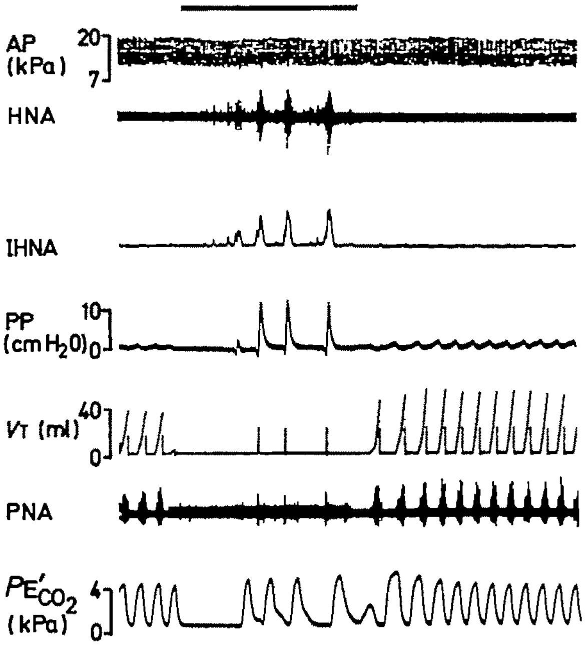

FIG 1. Changes in respiration and pharyngeal pressure during reflex swallowing elicited by stimulation of the SLN. Horizontal bar indicates a 30-s SLN stimulation period. AP = arterial pressure; HNA = hypoglossal nerve activity; IHNA = integrated hypoglossal nerve activity; PP = pharyngeal pressure; V_T = tidal volume; PNA = phrenic nerve activity; $P_{E'CO_2}$ = end-tidal carbon dioxide tension.

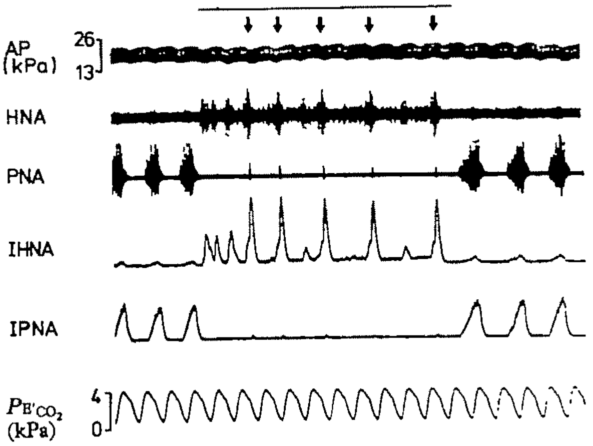

FIG 2 Changes in HN and PN activities during stimulation of the SLN in a vagotomized and paralysed animal. Swallows are indicated by arrows. IPNA = integrated phrenic nerve activity. (For other abbreviations, see legend to figure 1.)

Effects of increasing depth of anaesthesia on reflex swallowing

Since it was possible to identify the swallowing reflex from the characteristic PN and HN responses, the effects of increasing depths of anaesthesia on the swallowing reflex were investigated in vagotomized and paralysed animals. In this condition, possible effects of changes in Pa_{CO_2} and Pa_{O_2} as a result of apnoea and possible effects of vagal reflex could be eliminated.

Figure 3 shows an example of the effects of increasing depth of anaesthesia on PN and HN activities during SLN stimultion. At a light level of anaesthesia (baseline "control" state), stimulation caused a mixture of large amplitude bursts of HN, various forms of phasic HN bursts, and tonic HN discharges. The first swallowing reflex occurred with a latent period of 11 s and two acts of swallowing followed. With administration of 30% nitrous oxide, the latent period was prolonged considerably and only one act of swallowing occurred during continuing stimulation of the SLN. With further increases in the concentration of nitrous oxide, the swallowing reflex was no longer elicited. It can also be observed that both tonic HN discharges and various forms of HN discharges related to non-swallowing acts were depressed progressively as the depth of anaesthesia increased, although the former was more resistant to the depressant effects of anaesthesia than the latter.

The latent period and the number of swallows during SLN stimulation at different depths of anaesthesia obtained in all animals are listed in table I. The results indicate that increasing depth of anaesthesia caused progressive inhibition of the swallowing reflex. The progressive depression of the HN response, however, was not caused by a deterioration of motoneurones, since vigorous respiratory activity of HN was still observed in response to an asphyxic procedure, even with the inhalation of 70% nitrous oxide (fig. 4).

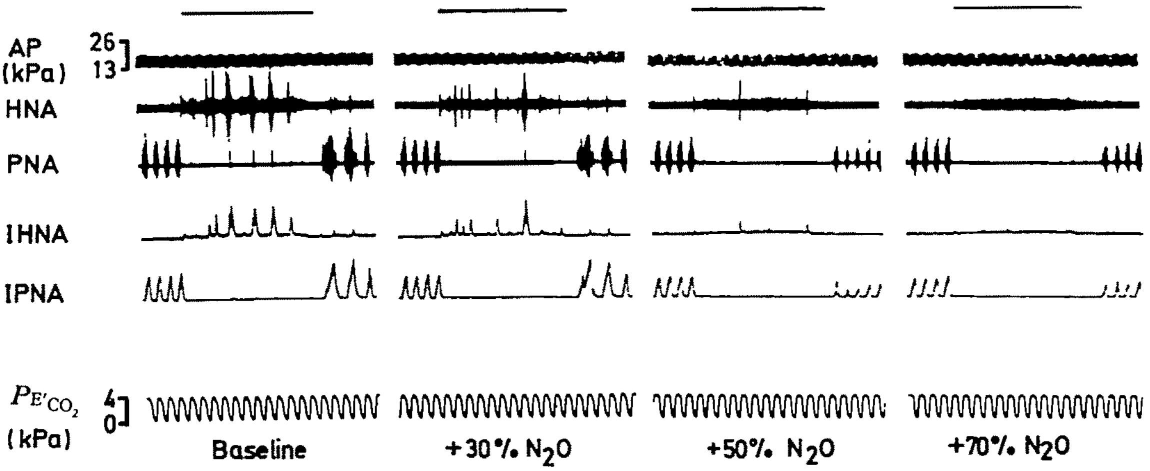

FIG. 3. Responses of HN and PN activities to stimulation of the SLN at different depths of anaesthesia Horizontal bars indicate 30-s periods of stimulation of the SLN

TABLE I. *Latent period (LP) for the initiation of reflex swallowing, and the number of swallows (No. of S) during stimulation of the SLN for 30 s. Significant differences from values of baseline:* $^*P < 0.05$; $^{**}P < 0.01$

	Baseline		+30% N_2O		+50% N_2O		+70% N_2O	
Cat No	LP (s)	No. of S	LP (s)	No. of S	LP (s)	No. of S	LP (s)	No. of S
1	5.0	6	7.5	2	19.5	1	>30	0
2	15.0	2	28.0	1	>30	0	>30	0
3	7.0	4	12.0	2	27.5	1	>30	0
4	15.0	3	19.5	2	>30	0	>30	0
5	13.0	3	18.0	2	23.0	1	>30	0
6	5.0	5	18.5	2	19.5	1	>30	0
7	11.0	3	22.0	1	>30	0	>30	0
8	12.0	3	26.0	1	>30	0	>30	0
9	10.0	4	12.0	2	>30	0	>30	0
10	8.5	3	19.0	1	28.5	1	>30	0
Mean ± SD	10.2 ± 3.7	3.6 ± 1.2	18.3 ± 6.8*	1.6 ± 0.5**	>19.5	0.5 ± 0.5**	>30	0**

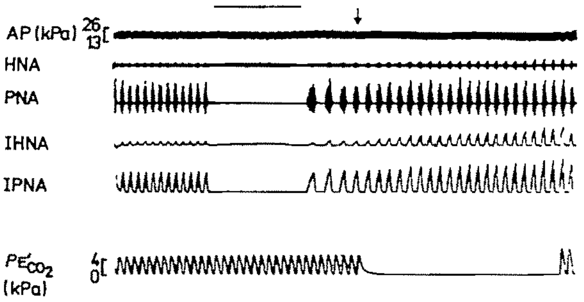

FIG 4 Effects of asphyxia on HN and PN activities during inhalation of 70% nitrous oxide. Note that stimulation of the SLN caused almost no activity in HN and PN, but both PN and HN activities increased progressively immediately following the procedure of asphyxia (the respirator was stopped at arrow)

To evaluate the effects of anaesthesia on the swallowing reflex, the threshold stimulus for the occurrence of the swallowing reflex at different depths of anaesthesia was determined; the results are summarized in table II. Inhalation of 30% nitrous oxide significantly increased the thresholds. However, once the swallowing reflex was elicited, the pattern and the amplitude of the activities of the nerves were essentially the same as those observed during the control state. In some animals, during inhalation of 50 and 70% nitrous oxide, the threshold values could not be determined since no response was produced at all, even with a stimulus 100 times that necessary to elicit the swallowing relex during the control state.

TABLE II. *Thresholds of stimulus intensity for the swallowing reflex. Significant differences from value baseline:* $^*P < 0.05$

Cat No.	Baseline	+30% N_2O	+50% N_2O	+70% N_2O
1	0.06 (V)	0.12 (V)	0.18 (V)	>6.0 (V)
2	0.04	0.10	>6.0	>6.0
3	0.06	0.14	0.20	>6.0
4	0.08	0.16	1.82	>6.0
5	0.10	0.18	0.30	>6.0
6	0.06	0.08	0.16	>6.0
7	0.06	0.10	0.50	>6.0
8	0.08	0.18	>6.0	>6.0
9	0.04	0.08	>6.0	>6.0
10	0.14	0.30	0.40	>6.0
Mean ± SD	0.07 ± 0.03	0.14 ± 0.07*	>0.16	>6.0

DISCUSSION

Although the neurophysiological definition of swallowing has been made by electromyography (Doty and Bosma, 1956), possible movement artefact as a result of electrode displacement in spontaneously breathing animals, may be disadvantageous. Moreover, electromyographic recordings are not applicable in paralysed animals—which permit more stable experimental conditions than do spontaneously breathing animals.

In the present study we have shown that the characteristic responses of HN and PN during SLN stimulation can be used as an indicator of the swallowing act even in paralysed and vagotomized animals. The brief and feeble discharge observed in PN during the swallowing act corresponds conceivably to the minor movement of the diaphragm known as "Schluckatmung" (Marckwald, 1889). Although its functional significance has been questioned (Doty, 1968), its consistent appearance during swallowing suggests that it is a part of the swallow synergism.

Characteristic discharges in HN observed during swallowing were monophasic or multiphasic in their configurations and were distinctly different from other phasic discharges observed during non-swallowing movements of the pharynx and the larynx. The latter discharges correspond conceivably with a variety of brief reflexes which have been designated "elementary" reflexes by Doty and Bosma (1956).

In agreement with the clinical observations that the swallowing reflex is blocked readily by anaesthesia, our results demonstrated that deepening anaesthesia (by the administration of nitrous oxide) progressively depressed the swallowing reflex. Obviously, the background anaesthetic (α-chloralose) might have exerted some influence on the results. Certainly, the values of the latent period for the initiation of reflex swallowing, and the number of swallows during the baseline state, were variable and may indicate that the baseline level of anaesthesia was slightly different in each animal. However, the effects of deepening anaesthesia on the swallowing reflex were consistent regardless of the variable responses during the control state and, therefore, it is unlikely that the presence of the background anaesthetic masked the effects of increasing depth of anaesthesia.

It seems that reflex swallowing is achieved by intricate co-ordination of neural mechanisms involving the sensory and motor nuclei and a specific neural group, the swallowing centre (Doty, 1968). Since the pattern of discharge of action potentials for swallowing is ultimately determined at the site of the individual motoneurone concerned, analysis of changes in motor discharges of HN in response to increasing depth of anaesthesia might present some information about the mechanisms of depression of the swallowing reflex produced by anaesthesia.

Detailed analysis of HN activity revealed that stimulation of the SLN produced three different responses in the HN. Although the large amplitude bursts in the HN characteristically observed during the act of swallowing were most sensitive to increasing depth of anaesthesia, once it was elicited, the pattern and the amplitude of HN activity were independent of the depth of anaesthesia. This finding is in agreement with the observation of Doty and Bosma (1956) who showed that administration of pentobarbitone i.v. caused considerable alterations in respiratory pattern, but was without effect on the organization of reflex swallowing, indicating the consistency of the motor pattern of the swallowing reflex. Various forms of phasic discharges related to non-swallowing acts were relatively resistant to increasing depth of anaesthesia, but deepening anaesthesia progressively depressed these discharges. Tonic discharges elicited by SLN stimulation were the most resistant to increasing depth of anaesthesia, although these discharges also seemed to be depressed by deepening anaesthesia in a dose-related manner. The different susceptibility to anaesthesia of these responses may suggest that the neural pathway relevant to each response has a different sensitivity to the depressant effect of anaesthesia. There is a possibility that the progressive depression of HN responses with deepening anaesthesia may result from the direct action of anaesthesia on hypoglossal motoneurones. However, the finding that vigorous respiratory activity emerged immediately in response to asphyxia, even during inhalation of 70% nitrous oxide where SLN stimulation caused little or no response in HN activity, indicates that the direct depression of hypoglossal motoneurones may not be the principal cause of the progressive depression of HN responses as a result of anaesthesia.

It is unlikely that any alteration in responsiveness occurred at the level of sensory receptors, since SLN was stimulated electrically with a constant frequency and intensity. Thus, it would seem that the alteration of HN responses is mediated at an internuncial level, where the interneurones link both the afferent and efferent parts of the reflexes.

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CHRONOTROPIC AND DROMOTROPIC EFFECTS OF ATROPINE AND HYOSCINE METHOBROMIDE IN UNANAESTHETIZED DOGS

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SUMMARY

Atrial pacing at progressively increasing frequencies was performed in 12 awake dogs through electrodes implanted aseptically in the right atrium and led out through the skin of the neck. Heart rate and the Wenckebach point (the minimum pacing frequency for which a second degree A–V block first appeared) were measured by electrocardiography. The responses of the sino–atrial and auriculo–ventricular nodes to atropine and hyoscine methobromide were characteristically bimodal. Slowing of the heart rate and atrioventricular conduction appeared with the lower doses of atropine (6.25 $\mu g\ kg^{-1}$ i.v) and hyoscine methobromide (0.4 $\mu g\ kg^{-1}$ i.v.); at doses of atropine 12.5 $\mu g\ kg^{-1}$ i.v. and hyoscine methobromide 1.56 $\mu g\ kg^{-1}$ i.v., only atrioventricular conduction was slowed; an acceleration of heart rate and atrioventricular conduction occurred in response to the higher doses of both drugs. These results show, in the awake dog, that the effects of atropine and hyoscine methobromide on heart rate and atrioventricular conduction are entirely comparable when appropriate doses are used, and reveal a difference in the responsiveness of the sino–atrial and auriculo–ventricular nodes to these drugs.

Small doses of atropine decrease heart rate while larger doses increase it (Harris, 1921; McGuigan, 1921; Danielopolu, 1924). Accordingly, in man very slow injections i.v., or injections i.m. or s.c. induce a bimodal effect: a period of bradycardia followed by characteristic tachycardia as the dose is increased.

Atropine-induced tachycardia is known to be accompanied by a facilitation of atrioventricular (A–V) conduction (Bisett, de Soyza et al., 1975). Facilitation of A–V conduction has also been reported during the initial phase of bradycardia (Dauchot and Gravenstein, 1970; Das, Talmer and Weissler, 1975). The occurrence of A–V dissociation was reported in man by Wilson as early as 1915, and described subsequently in man (Averill and Lamb, 1959; Jones, Deutsch and Turndorf, 1961), and in the unanaesthetized dog (Muir, 1978).

The present investigation compared, in the unanaesthetized dog, the effects of atropine on heart rate (HR) and A–V conduction as assessed in terms of the Wenckebach point (WP) for 2 h following administration.

In view of the fact that atropine-induced bradycardia has been attributed at least partly to stimulation of vagal centres (Heinkaup, 1922; Katona, Lipson and Dauchot, 1977), the effects of atropine were compared additionally with those of the anticholinergic agent hyoscine methobromide (MS) which has limited ability to cross the blood–brain barrier (Domino and Corssen, 1967).

MATERIALS AND METHODS

Twelve mongrel dogs weighing on average 15 ± 2 kg were studied. Following thoracotomy under anaesthesia with pentobarbitone 25 mg kg^{-1} i.v., two-wired stainless steel surgical electrodes (Laboratoires Bruneau, France) were implanted in the wall of the right atrium. The two electrodes were placed on either side of the sino–atrial node 2 cm apart. The free ends of the electrodes were tunnelled out through the nape of the animal's neck. The dogs were given penicillin for 3 days.

After recovery, the dogs were trained to remain calm on an examination table in the presence of one

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investigator. Pharmacological testing began 10–15 days after surgery. An electrocardiogram was recorded (three standard leads: Cardiopan T3). The right atrium was paced at progressively increasing frequencies using a Jansen stimulator (Sid Serial no. F 00058). The Wenckebach point (WP) was determined by increasing the driven atrial frequency by 10 beat min^{-1} every min until second degree type I A–V block first appeared. All stimuli were obtained with a 2-ms duration rectangular pulse and twice the initial diastolic threshold voltage.

Before testing, a catheter was placed in a cephalic vein. Three control values of the WP were determined before injection, at 5 and 20 min after injection and finally every 20 min for 2 h.

Atropine as sulphate and hyoscine methobromide as sulphate were diluted in 0.9% sterile saline. Doses are in terms of the salt. Atropine was given in doses of 100, 25, 12.5 and 6.25 µg kg^{-1} i.v. and hyoscine methobromide in doses of 25, 6.25, 1.56, 0.8 and 0.4 µg kg^{-1} i.v. in random order to groups of six dogs. This range of doses covered direct stimulating and blocking actions on the muscarinic receptors.

Propranolol hydrochloride 1 mg kg^{-1} in distilled water was given alone, and in combination with atropine 100 µg kg^{-1} i.v. to block cardiac β_1-adrenergic or muscarinic receptors, or both, and to evaluate the role of sympathetic tone in the unanaesthetized dog. Values of HR and WP are in beat min^{-1} ± SEM.

Statistical significances of the effects of the drugs, as a function of time, upon HR and WP were calculated by two-factor analysis of variance followed by a Student Fisher *t* test.

RESULTS

Control values (table I)

Injection of 5 ml of sterile saline modified neither HR nor WP which remained stable throughout the 2-h period of observation.

Propranolol 1 mg kg^{-1} affected HR only slightly and inconsistently; no significant effect on WP was observed.

Following propranolol, atropine increased the HR from 81 ± 7 to 187 ± 12 beat min^{-1} (5th min) and WP from 116 ± 7 to 340 ± 13 beat min^{-1} (5th min) ($P < 0.001$), the increases remaining significant throughout the study.

Effects of atropine (fig. 1)

Atropine 100 µg kg^{-1} increased HR and WP significantly throughout the period of observation. HR increased from 113 ± 12 to 217 ± 15 beat min^{-1} after 5 min and to 153 ± 10 beat min^{-1} by the 120th min. WP increased from 142 ± 11 to 341 ± 11 beat min^{-1} after 5 min and reached 312 ± 29 beat min^{-1} by the 120th min.

Atropine 25 µg kg^{-1} increased HR from 108 ± 6 to 155 ± 8 beat min^{-1} after 5 min and to 116 ± 6 beat min^{-1} by the 120th min. WP increased from 139 ± 6 to 310 ± 6 beat min^{-1} after 5 min and reached 164 ± 6 beat min^{-1} after 120 min. All increases were significant.

With doses of atropine 12.5 µg kg^{-1}, except for a slight cardioacceleration at the 5th min, HR remained close to control values throughout. However, three dogs had second degree A–V block for 4 min after injection (fig. 2), and at the 5th min WP

TABLE I. *Effects of physiological saline, propranolol and autonomic blockade on heart rate (HR) and Wenckebach point (WP) in unanaesthetized dogs. Data expressed as mean ± SEM obtained from six dogs. Significant difference from corresponding means of the basal values:* *P < 0 05; ** P < 0.01; ***P < 0.001

		Time (min)						
	Basal	5	20	40	60	80	100	120
Saline 5 ml (control group)								
HR	88 ±11	89 ±10	89 ±10	89 ±8	89 ±8	90 ±9	92 ±10	87 ±9
WP	137 ±14	136 ±9	135 ±9	137 ±13	137 ±8	136 ±8	134 ±10	142 ±14
Propranolol 1 mg kg^{-1}								
HR	92 ±10	91 ±9	83 ±8*	85 ±9	86 ±11	83 ±9*	83 ±10*	86 ±10
WP	124 ±13	119 ±13	119 ±13	121 ±13	129 ±15	133 ±20	131 ±18	135 ±15
Atropine 100 µg kg^{-1} after propranolol								
HR	81 ±7	187 ±12***	188 ±12***	182 ±12***	178 ±14***	172 ±12***	162 ±12***	148 ±12***
WP	116 ±7	340 ±13***	342 ±13***	319 ±15***	291 ±12***	279 ±21***	271 ±8***	278 ±24***

was substantially lower than control, and remained significantly reduced (initial value 134 ± 10 beat min^{-1}, decreasing to between 117 ± 9 and 115 ± 6 beat min^{-1}).

With atropine 6.25 μg kg^{-1} both HR and WP decreased significantly: HR from 91 ± 6 to 84 ± 7 beat min^{-1} after 5 min and to 80 ± 6 beat min^{-1} after 120 min; WP from 133 ± 10 to 114 ± 3 beat min^{-1} after 5 min and to 112 ± 7 beat min^{-1} after 120 min.

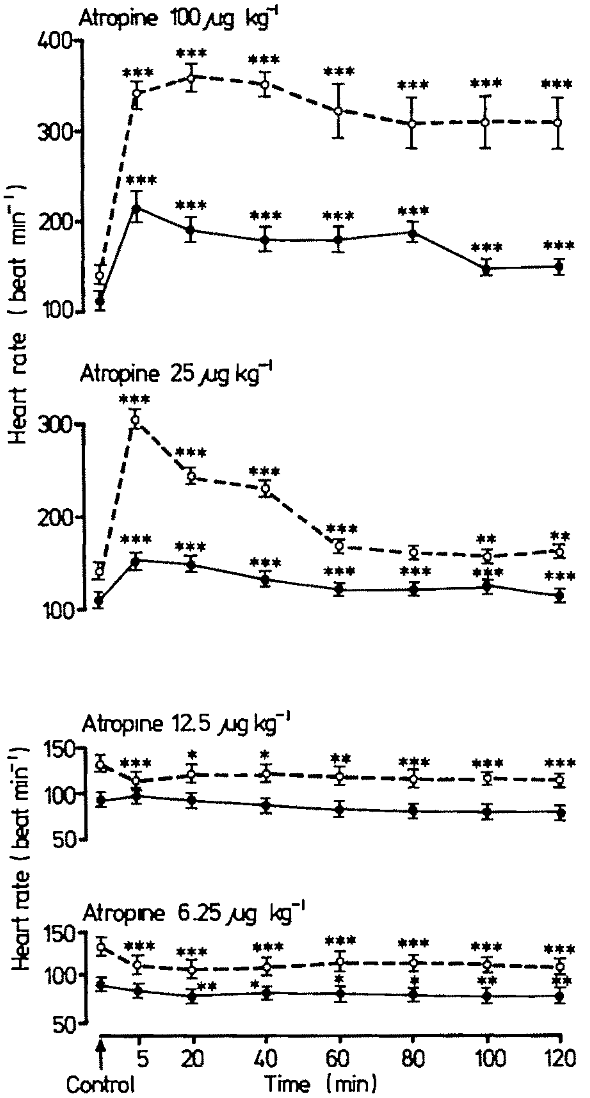

FIG 1. The effects of atropine 100, 25, 12.5 and 6 25 μg kg^{-1} on Wenckebach point (O– – –O) and heart rate (●——●) in unanaesthetized dogs ($n = 6$). Changes significantly different from control. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. The vertical bars represent SEM. The significant increases appeared in the Wenckebach point and heart rate at 100 and 25 μg kg^{-1} i.v. With atropine 12.5 μg kg^{-1} i v., decrease in Wenckebach point was significant, whereas there was no significant change in heart rate. Significant decreases appeared in the Wenckebach point and heart rate at 6.25 μg kg^{-1} i.v.

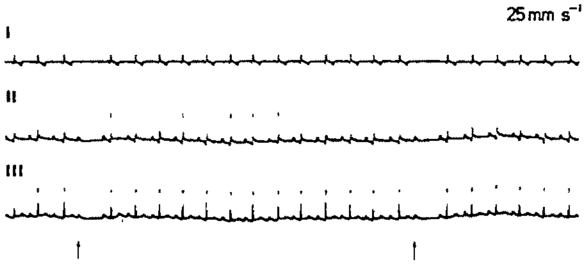

FIG 2. Electrocardiogram (lead I, lead II and lead III) modification obtained 4 min after the i.v. administration of atropine 12.5 μg kg^{-1} i.v in unanaesthetized dogs. Second degree atrioventricular block is shown by the absence of a QRS complex following the P waves (arrows).

Effects of hyoscine methobromide (fig. 3)

Hyoscine methobromide 25 μg kg^{-1} gave effects comparable to those of atropine 100 μg kg^{-1}. HR and WP increased significantly throughout the period of observation: HR from 105 ± 8 to 215 ± 9 beat min^{-1} by the 5th min, and WP from 137 ± 9 to 313 ± 16 beat min^{-1} by the 5th min.

With 6.25 μg kg^{-1}, HR increased from 100 ± 14 to 183 ± 10 beat min^{-1} after 5 min and remained significantly higher than control for 100 min. WP increased from 131 ± 17 to 310 ± 9 beat min^{-1} and remained close to that value throughout.

Hyoscine methobromide 1.56 μg kg^{-1} increased HR from 92 ± 5 to 98 ± 8 beat min^{-1} by the 5th min; HR remained significantly higher than the control values for 40 min. Second-degree A–V block appeared in all dogs during the first 4 min after injection (fig. 4). At the 5th min, WP was only slightly greater than HR. Subsequently, the time course of the WP values was parallel to that of HR. At the 20th and 40th min, WP was significantly higher than control, increasing from 129 ± 8 to 152 ± 8 and 146 ± 6 beat min^{-1}, and then decreasing gradually.

HR did not change through the administration of hyoscine methobromide 0.8 μg kg^{-1}. However, second degree A–V block developed in two dogs for 4 min after injection. WP was decreased but the changes were not significant.

Hyoscine methobromide 0.4 μg kg^{-1} induced a progressive reduction in HR which became significant only at the 40th min (from 94 ± 3 to 83 ± 4

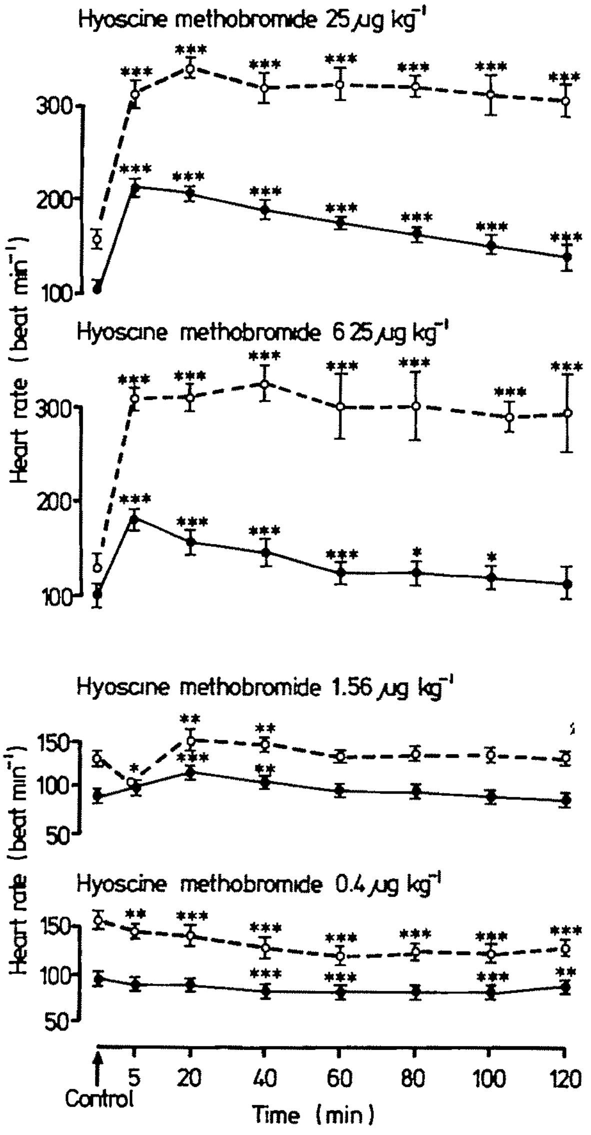

FIG 3. The effects of hyoscine methobromide 25, 6.25, 1 56 and 0.4 $\mu g\ kg^{-1}$ i.v. on Wenckebach point (o– – –o) and heart rate (•——•) in unanaesthetized dogs ($n = 6$). Changes significantly different from control: $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0\ 001$ The vertical bars represent SEM Significant increases appeared in the Wenckebach point and heart rate with 25, 6.25 and 1.56 $\mu g\ kg^{-1}$ i.v. With 1.56 $\mu g\ kg^{-1}$ i.v , Wenckebach point decreased sharply (5 min), increased significantly at 20–40 min then returned to control value. The significant decreases appeared in the Wenckebach point and heart rate with 0.4 $\mu g\ kg^{-1}$ i v.

beat min^{-1}). WP decreased also (from 155 ± 6 to 145 ± 7 beat min^{-1} after 5 min), and reached a minimum of 130 ± 8 beat min^{-1} by the 60th min.

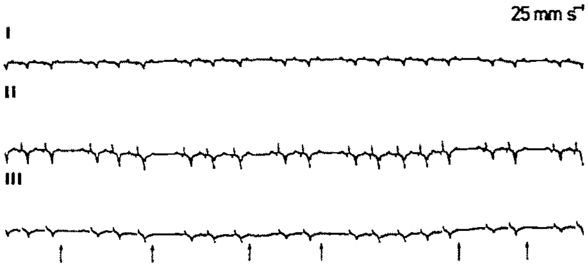

FIG 4. Electrocardiogram (lead I, lead II and lead III) modification obtained 4 min after the i.v. administration of hyoscine methobromide 1 56 $\mu g\ kg^{-1}$ i.v. in unanaesthetized dogs. Second degree atrio–ventricular block is shown by the absence of a QRS complex following the P waves (arrows).

DISCUSSION

Atrial pacing with progressively increasing frequency (Arnould et al., 1963; Scherlag et al., 1969) was preferred to the method of extrastimulus (Krayer, Mandoki and Mendez, 1951; Moe, Preston and Burlington, 1956), the reason for this choice in the unanaesthetized dog having been detailed in a previous study (Duchêne-Marullaz et al., 1982). Both methods, according to Bisset, Kane and colleagues (1975) give comparable results in functional investigations.

Under our experimental conditions, the vagi would appear to exert a strong inhibitory influence on the canine cardiac pacemaker as suggested by the positive cardiac chronotropic effect of atropine or hyoscine methobromide in intact or propranolol-pretreated animals. Thus, it follows that, in the unstressed dog, the intrinsic (in the absence of autonomic control) firing frequency of the sinus node is greater than the basal rate. In contrast, the sympathetic contribution to baseline heart rate in the presence of vagal tone was minimal, as indicated clearly by the effects of propranolol given alone.

The effects of atropine on heart rate in the dog are entirely comparable to those observed in man, provided the dog is not anaesthetized (Muir, 1978). Low blood concentrations following injection of small doses, slow i.v. injections, and s.c. or i.m. injections which release atropine only slowly into the bloodstream, induce bradycardia (Harris, 1921; Morton and Thomas, 1958; Kottmeier and Gravenstein, 1968). Higher blood concentrations induce tachycardia. Anaesthesia with chloralose (Kottmeier and Gravenstein, 1968) prevents this bradycardiac phase from being seen in the dog.

The mechanism of this bradycardia is unclear. It has been suggested (Katona, Lipson and Dauchot, 1977) that it might arise, at least in part, from stimulation of vagal centres. However, such a postulate is in contradiction to the fact that bradycardia still occurs after bilateral vagotomy (Duchêne-Marullaz, Arnould and Schaff, 1963; Kottmeier and Gravenstein, 1968), and that a comparable effect may be obtained with agents which do not cross the blood–brain barrier, such as atropine methyl bromide (Kottmeier and Gravenstein, 1968; Fennell et al., 1979) methyl-atropine nitrate (Graham and Lazarus, 1940) or hyoscine methobromide (Fenell et al., 1979). Thus, the bradycardiac effects of atropine that persist for days after vagotomy may still result from inhibition of acetylcholinesterase, since the post-ganglionic vagal nerves that are not affected by the vagotomy may still show spontaneous release of acetylcholine. Our results show that a similar degree of bradycardia is obtained with either atropine 6.25 $\mu g\ kg^{-1}$ or hyoscine methobromide 0.4 $\mu g\ kg^{-1}$. Atropine has also been shown to inhibit the activity of cholinesterase (Sekiya, 1954; Kato, 1971) and it has been postulated that, with small doses, this anticholinesterase activity may predominate and, thus, lead to enhanced response of the receptor to naturally-existing acetylcholine. However, if this were the case, the bradycardia produced by atropine would disappear a few days after bilateral vagotomy, and this has not been observed (Duchêne-Marullaz, Arnould and Schaff, 1963).

It is difficult to say whether a direct effect on pacemaker cells is involved or rather an action on the cholinergic receptors themselves. According to Patton (1960), most receptor-blocking agents in small doses produce transient depolarization of the receptors, resulting in stimulation. However, with the smallest doses of atropine and hyoscine methobromide used in our experiments, the bradycardia was far from brief (more than 2 h). It has been shown (Duchêne-Marullaz et al., 1982) that, under similar experimental conditions, the injection of 5 ml of sterile saline solution modifies neither HR nor WP over a 2-h period in well-trained dogs. Thus, the bradycardia induced by atropine and hyoscine methobromide is evidently a persistent vagomimetic effect.

With the smallest doses used, this vagomimetic effect occurred concurrently at both the S–A and A–V nodes. This finding is at variance with the observations of Dauchot and Gravenstein (1970) and Das, Talmer and Weissler (1975), according to whom A–V conduction is facilitated even at doses low enough to decrease HR. Our results indicate that such dissociation of HR and A–V conduction occurs only briefly after injection. Thus, with atropine 12.5 $\mu g\ kg^{-1}$ HR increased at the 5th min while WP was decreased significantly. Thereafter, WP remained decreased, whereas HR decreased gradually to values lower than control. Similarly, hyoscine methobromide 1.56 $\mu g\ kg^{-1}$ increased HR significantly at the 5th, 20th and 40th min, but induced second-degree A–V block immediately after injection and a significant decrease in WP by the 5th min.

Under certain circumstances, atropine may shift the site of A–V block. Atropine may change the site of block from the A–V node to the His–Purkinje system. Sinus acceleration and enhanced A–V nodal conduction result in shorter H–H intervals and atropine has no direct enhancing effect on His–Purkinje conduction (Aktar et al., 1974). At relatively low driving rates, the functional refractory period of the Purkinje system can exceed that of the A–V node and premature beats may fail to traverse the Purkinje system for this reason (Spear and Moor, 1971). Atropine and hyoscine methobromide contribute to this by providing the prerequisite balance between nodal conduction velocity and refractoriness within the A–V node. Consequently, A–V block may emerge during atrial acceleration. Thus, we consider that the limit of stimulation and blocking action on the muscarinic receptors of the heart was probably obtained near atropine 12.5 $\mu g\ kg^{-1}$ and hyoscine methobromide 1.56 $\mu g\ kg^{-1}$. However, at the 20th and 40th min, tachycardia was associated with facilitated A–V conduction. Thus although, in general, the effects of atropine and hyoscine methobromide on S–A and A–V nodes are in the same direction, effects in the opposite direction may occur immediately after injection. A difference in sensitivity of the muscarinic cholinoceptors of the S–A and A–V nodes has been reported. Musgrave, Branch and Beckett (1981) showed that, in the unanaesthetized dog, the A–V node was 1.9 times more sensitive to acetylcholine than the S–A node. The cholinesterase concentration is, moreover, greater in the A–V node than in the S–A node (James and Spence, 1966). The fact that hyoscine methobromide-induced tachycardia decreased gradually, whereas the WP remained stable over 2 h after 25 and 6.25 $\mu g\ kg^{-1}$ injection does not indicate a differential sensitivity of the S–A and A–V nodes. There is considerable evidence that the tachycardia produced by atropine is much greater than that produced by vagotomy or ganglionic blocking drugs (Brunsting et al., 1979).

More importantly, Loeb, Dalton and Moran (1981) have observed that the negative chronotropic effect of acetylcholine at the S–A node is decreased during vagal stimulation, whereas the negative dromotropic effect on A–V nodal conduction remains unaltered. It has been observed also, that continuous infusion of atropine fails to maintain HR at the same value; induced cardio-acceleration decreases even though the blood concentration of atropine increases (Chassaing et al., 1979). No analogous investigation of the time course of A–V conduction during the infusion of atropine has been reported. Nonetheless, the results obtained here with hyoscine methobromide 25 and 6.25 $\mu g\ kg^{-1}$ suggest that blockade of A–V nodal cholinoceptors is likely to be more stable.

In spite of these few differences, and of the fact that A–V blockade does not preclude tachycardia, S–A and A–V nodes evidently respond in much the same way to atropine and hyoscine methobromide. A negative chronotropic effect is generally accompanied by a negative dromotropic effect.

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INFUSION THROMBOPHLEBITIS

G. B. H. LEWIS AND J. F. HECKER

SUMMARY

Infusion thrombophlebitis is a common complication of i.v. infusions. Many factors appear to be involved in its aetiology, of which the duration of infusion, the drugs infused and the solution(s) infused are the most important. Effective prophylaxis should be based on an understanding of the possible pathophysiology.

An i.v. infusion is the most commonly performed surgical procedure in hospital wards (Eremin and Marshall, 1977) and is a frequently used therapeutic regimen for hospitalized patients encompassing the entire spectrum of patient population and disease (Arnold, Elliott and Holmes, 1977). Infusion thrombophlebitis (ITP) is the most common complication of i.v. infusion (Curry and Zallen, 1973; Arnold, Elliott and Holmes, 1977; Eremin and Marshall, 1977) and is characterized by a painful local reaction often accompanied by erythema and oedema (Chamberland, Lyons and Brock, 1977). Symptoms and signs usually lasts days or weeks, although Hästbacka and colleagues (1965) reported that symptoms may persist for months. It is possible for suppuration (Ross, 1972; Curry and Zallen, 1973; Arnold, Elliott and Holmes, 1977), septicaemia (Arnold, Elliott and Holmes, 1977) and rarely pulmonary embolism (Swanson and Aldrete, 1969) or death (Frazer, Eke and Laing, 1977) to result.

Warthen (1930) was perhaps the first to describe the condition: "About the third or fourth day the vein wall becomes oedematous and painful from the constant flow of dextrose, which is mildly irritating. The lumen of the vessel is decreased by this oedema and the flow gradually diminishes." This succinct description remains as true today as it was over 50 years ago.

CLINICAL DEFINITION

There is a spectrum of definitions in the literature as illustrated by the following:

(1) "Redness and tenderness and oedema of the vein" (Medical Research Council subcommittee, 1957; Skajaa et al., 1961; Thayssen, 1973; Hessov et al., 1977).

(2) "Tenderness and/or erythema along the vein, incurred up to 14 days after the infusion" (Hästbacka et al., 1965).

(3) "The polyethylene catheter was removed when a site was no longer judged to be viable because of pain, tenderness, oedema or inability to receive the prescribed fluids." (Daniell, 1973—who did not diagnose thrombophlebitis before this stage).

(4) Dinley (1976) modified the (British) Medical Research Council (1957) criteria as follows:

Grade 0 "No reaction or discomfort, puncture wound clean."

Grade 1 "Induration around the vein. Slight tenderness may be present at the infusion site. No pain on speeding up the infusion rate and no evidence of phlebitis."

Grade 2 "Mild discomfort at the infusion site, tenderness over cannula and just proximal to it. Slight discomfort on increasing the infusion rate. Erythema around the cannula site, but not extending beyond the tip of the cannula."

Grade 3 "Moderate discomfort at the intravenous site. Constant moderate to severe pain when the intravenous rate is increased. Erythema extending to less than five cms. proximal to the tip of the cannula."

Grade 4 "Moderate to severe discomfort at the

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TABLE I. *Incidence of infusion thrombophlebitis*

Year	Author(s)	Incidence (%)	Comment
1951	Bolton-Carter	52	
1952	Handfield-Jones and Lewis	68	
1952	Page, Raine and Jones	65	
1954	Jones	73	
1957	Medical Research Council	56	
1959	McNair and Dudley	100	Long saphenous veins
1961	Skajaa and colleagues	71	
1965	Hastbacka and colleagues	25	Of 1048 infusions
1966	Elfving and Saikku	18	
1967	Kay and Roberts	17	
1969	Swanson and Aldrete	7.4–47.9	Depending on needle size
1972	Pussell and Pitney	75	^{125}I detection
1972	Ross	35	Of 35 infusions
1975	Collin and colleagues	43.2	Over 72 h
1976	Dinley	49.4	
1976	Stephen and colleagues	31	
1977	Arnold, Elliott and Holmes	12	
1977	Chamberland, Lyons and Brock	63	
1977	Eremin and Marshall	43	Without buffering pH
1977	Frazer, Eke and Laing	4.3 at 24 h; 100 at 5 days	
1977	Hessov and colleagues	6.1	
1981	Boon and colleagues	36	

intravenous site. Infusion usually markedly slowed or ceased spontaneously. Erythema greater than five cms. proximal to the tip of the cannula.”

Grade 5 “As for grade 4, but pus seen at the infusion site on removal of the cannula.”

The accumulation of ^{125}I-labelled fibrinogen, which is an accurate and sensitive method of detecting leg vein thrombosis (Kakkar et al., 1969) was used by Pussell and Pitney (1972) to detect i.v. cannula thrombosis 24–48 h before any clinical evidence of reactions such as tenderness, inflammation and swelling. This more objective method of diagnosing thrombosis showed an overall incidence of 75% at i.v. cannula sites, but suffers from the disadvantage that the development of ITP may not necessarily involve thrombosis.

The most comprehensive of these definitions is that of Dinley (1976). It suffers from the disadvantage that not all of the signs may develop or develop in the sequence indicated. For ward use, the first two are possibly preferable.

INCIDENCE

The incidence of ITP varies widely (table I), reflecting the lack of a standard clinical definition. In addition, the reported duration of phlebitic signs varies widely (table II).

Unless the infusion site is examined regularly for 2 weeks and all diagnosed cases followed until symptoms have disappeared, a false impression of the incidence, and especially severity and duration, may be gained. Many patients subsequently fail to report any symptoms which develop. Patients may sometimes only admit to symptoms suggestive of mild ITP on specific questioning. These patients may state that they regard the development of a tender swelling in the region of their infusion site as “to be expected”. There may be many mild cases of ITP

TABLE II. *Duration of infusion thrombophlebitis*

Series	Duration
Gjares (1957)	49% < 1 week 44% > 2 weeks 30% > 1 month 1% > 6 months
Skajaa and colleagues (1961)	May persist for many weeks
Eerola and Pontinen (1964)	Average 53 days
Hastbacka and colleagues (1965)	Average 28 days Maximum 7 months 15% < 2 weeks
Pederson (1970)	May remain for some days or weeks, thus prolonging convalescence

which last for a short time and are never reported. Experience with more than 10 000 infusions suggests that these venous reactions would correspond to Grade 1 or Grade 2 used in Dinley's (1976) series.

PATHOLOGY

Pathophysiology

Rudolf Virchow (cited by Little, Loewenthal and Mansfield, 1974) suggested, more than 100 years ago, that thrombus formation might result from:

(1) changes in the blood,
(2) changes in the characteristics of the flow of the blood,
(3) changes in the vessel wall.

These postulates continue to form the basis of modern thinking, with particular emphasis on the possible changes in the blood (Little, Loewenthal and Mansfield, 1974).

It has been suggested that chemical irritation causes much of the inflammation in ITP (Jones, 1954; Eerola and Pöntinen, 1964; Hästbacka et al., 1965; Elfving and Saikku, 1966; Fonkalsrud, Murphy and Smith, 1968). Prostaglandins may be released or stimulated by histamine, adenosine-5-triphosphate (ATP) and prostaglandin E_1 during the inflammatory response (Chahl and Chahl, 1976). Prostaglandins PGE_1 and PGE_2 increase local vascular permeability via histamine and 5-hydroxtryptamine in rat and man (Crunkhorn and Willis, 1971). The early histological changes observed by Ghildyal, Pande and Misra (1975), namely swelling of endothelial cells and polymorphonuclear (PMN) leucocytic infiltration to the tunica media, could perhaps be initiated by the metabolites of arachidonic acid. When the vein wall is injured, platelet phospholipase A_2 is stimulated to form biologically active compounds PGE_2 and PGD_2 which increase vascular permeability and hydroxyeicosatetraenoic acid (HETE) and thromboxane B2 (TXB_2) which are chemotactic for PMN leucocytes (Moncada and Vane, 1978). PGG_2, PGH_2 and thromboxane A_2 are other platelet-produced arachidonic acid metabolites which are active as platelet aggregating or releasing agents and which may also be involved at the endothelial surface.

Humoral agents released in response to venous irritation may provoke venoconstriction. If the flow of blood in the vein is diminished, irritant infusates are not rapidly diluted with blood and this, together with stasis, would predispose to ITP. Sharpey-Schafer and Ginsburg (1962) studied the effects of humoral agents on venous tone. Adrenaline, noradrenaline, 5-hydroxytryptamine and histamine all increased venous tone in the forearm. Nitrite decreased tone whilst increasing forearm blood flow. Mason and Braunwald (1965) observed the effect of sublingual nitroglycerine on the human forearm venous tone. Forearm blood flow was increased whilst forearm vascular resistance and venous tone were decreased.

It is possible that the local application of nitroglycerine ointment near the site of an i.v. infusion may prevent or reduce the effects of released humoral venoconstricting substances, increase blood flow and prevent or delay the onset of ITP. Hecker, Lewis and Stanley (1983) have demonstrated the effectiveness of very small applications of nitroglycerine ointment on the dorsum of the hand as a local venodilator before venepuncture. Nitroglycerine stimulates the synthesis of prostacyclin by cultured human endothelial cells (Levin et al., 1981). Prostacyclin is a very potent inhibitor of platelet aggregation and is synthesized in vascular walls by prostaglandin endoperoxides (Gryglewski et al., 1976). It was suggested by Moncada and Vane (1977) that, when a vessel is injured, endothelial damage could reduce prostacyclin synthesis, resulting in regional vasoconstriction. The potent vasoconstrictor thromboxane A_2 is then produced by aggregating platelets in the damaged area. Prostacyclin, which also relaxes smooth muscle cells in vein walls, may be produced in increased amounts by surrounding undamaged endothelial cells. The maintenance of effective prostacyclin concentrations in veins where infusions are sited may help to relax smooth muscle, preventing venoconstriction and platelet aggregation and possibly ITP.

The leukotrienes are a newly recognized group of biologically active mediators derived from arachidonic acid. There are several reasons why it is logical to suggest that these interesting compounds may be involved in the development of ITP. Leukotrienes may be produced by incubating arachidonic acid with polymorphonuclear leucocytes (Samuelsson, 1980) and these cells infiltrate vein walls as ITP develops. Leukotrienes possess potent pharmacological actions on smooth muscle and could possibly affect venous tone and the flow rates of infusion. In a recent study (Denis et al., 1982) leukotrienes were found to increase vascular permeability in the skin of guineapigs—relevant, as oedema is a prominent sign in clinical ITP.

Thrombi can form in any area of the cardiovascular system, the site influencing the thrombus size, composition and shape. Sodeman and Sodeman (1967) state that in phlebothrombosis the thrombus results from slowing of the blood stream and increased coagulability of the blood rather than from inflammation, whereas thrombophlebitis results from inflammation of the venous wall. They note that not all agree that phlebothrombosis and thrombophlebitis are sharply defined entities. Little, Loewenthal and Mansfield (1974), describing superficial phlebitis, make the following observations. The superficial veins of the limb are affected, there is thrombus within the lumen of the vein and an acute inflammatory reaction in the vein wall and in the surrounding tissues which results in pain.

Perhaps the frequently sketchy coverage accorded ITP in surgical and anaesthetic texts reflects the relative paucity of sound scientific papers on this subject. This review may assist to demonstrate the high incidence, inadequately understood pathogenesis, continuing morbidity and relative failure of prophylactic and therapeutic measures currently used in this iatrogenic condition.

Even less clear is the relationship of the pathology if ITP to the other frequent problem with infusions, that of extravasation of infusate ("tissuing").

Histopathology of superficial thrombophlebitis

Histopathological study of human veins following ITP has been limited (Thomas, Evers and Racz, 1970). A small piece of vein was removed under local anaesthesia from each of 50 patients with ITP by Ghildyal, Pande and Misra (1975), who also studied bacteriologically the tips of catheters, needles and other infusion devices. Histological changes were categorized as mild, moderate or severe. Mild changes in 23 specimens consisted of swelling of endothelial cells and PMN leucocyte infiltration in the tunica media. A further 18 specimens displayed cellular destruction and cellular breakdown of the endothelium. Oedema, PMN leucocyte infiltration and pyknotic nuclei of muscle cells were seen in the tunica media. The remaining nine were severely affected, with destruction of endothelium, cell nuclei pyknosis in the media with oedema and PMN leucocytic infiltration. Additionally, there was haemorrhage and necrosis of the wall. The damage was most severe when a thrombus was present. Five positive cultures of catheters or i.v. devices grew either *Staphylococcus aureus* (two), *Streptococcus haemolyticus* (two) or *Pseudomonas pyocyanea* (one). The authors concluded that there was little or no correlation between the bacterial cultures and phlebitis in their study. The changes in the vein were similar to earlier observations, including those of Gritsch and Ballinger (1959), who studied tissue reactions of dogs in which i.v. plastic tubing had been implanted.

Animal studies of ITP are also limited. Horvitz, Sachar and Elman (1943), who studied the veins of 11 dogs after infusions of 5% and 10% glucose solutions, found vacuolation of endothelial cells, followed by progressive cellular breakdown, leading to death of cells and destruction of the lining. Fibrin and thrombus were often deposited on the denuded subintima.

ITP was induced in dogs by i.v. infusion of dextrose saline to which, in some cases, repeated doses of naftidrofuryl (Praxilene) had been added by Woodhouse (1980). The infusions were continued for up to 12 h before sacrifice of the dogs. Histological examination showed early changes after 6 h in all specimens. More severe changes were noted in dogs sacrificed later. The infusions to which naftidrofuryl had been added produced only marginally more severe and earlier changes than dextrose/saline control infusions. In the early stages, histological examination showed fibrin and PMN leucocyte adherence to the endothelium of the vein. As the severity increased, leucocyte infiltration through the endothelium occurred, progressively affecting the deeper layers to the adventitae. Thrombosis was noted in three of 16 veins. Woodhouse concluded that the essential event in ITP is infiltration of the vein wall by circulating leucocytes.

Woodhouse (1980) and Ghildyal, Pande and Misra (1975) are in agreement that ITP is usually an acute sterile inflammation and the early study of Horvitz is consistent with this view.

Suppurative thrombophlebitis

There is a separate condition of suppurative thrombophlebitis which may be associated with cut-down infusions (Woodhouse, 1980). A brief review of the features of this serious complication is indicated, to define more clearly the differences between the two conditions. It is possible a previously sterile ITP may become infected and develop into suppurative thrombophlebitis.

Stein and Pruitt (1970) studied 295 patients, admitted to hospital with burns, in whom venous cannulations were performed by cut-down. Suppurative thrombophlebitis developed in 24 patients, in only 11 of whom was the diagnosis made before death. Fever was present in 10 of the 11. Six patients had exudation of purulent material from the vein. Pain, tenderness, a red streak and swelling, common findings in ITP, were rare in this series. In 14 patients no excision was performed; 13 were diagnosed at autopsy and the one case treated conservatively with antibiotics, elevation, warm compresses and dextran, died of septicaemia. Of the other 10 patients who were treated by extensive excision of the involved vein, seven survived. If the diagnosis is in doubt, exploratory venotomy is recommended.

Stein and Pruitt (1970) claimed that this condition was responsible for 2.4% of deaths. They proposed the following sequence to explain the clinical and histological findings. Firstly, an i.v. cannula is sited in a vein and a fibrin clot forms on the vein wall or catheter tip. Subsequently, micro-organisms are trapped in the clot when they enter the vein via the cannula or venous tributaries. Finally, the infected clot serves to seed the blood-stream with micro-organisms. Patients with thermal injury are notoriously prone to infection, and scrupulous attention to asepsis is constantly emphasized, but any evidence suggestive of suppuration associated with i.v. therapy in a patient is necessarily viewed with con-

TABLE III. *Duration of infusion*

Series and year	Duration of infusion (h) and ITP 0	6	12	24	48	96	192
Bolton-Carter (1951)	<-------------| 4.5%	 |-------------------->		 52%			
Bogen (1960)	<------------------------|	 0.9%		|---------------|	 37.5%		
Cheney and Lincoln (1964)	<-----------------------------------|	 9%		 |--------------->		 58%	
Eerola and Pontinen (1964)	<----- ----->	25.9% overall incidence av. 4–5 h					
Hastbacka and others (1965)	<--|	 62% of ITP occurred in first week					
Kay and Roberts (1967)	<-------------|	 (low) |----------------------->			 (high)		
Swanson and Aldrete (1969)	<-----------------------|	 20% of ITP		 |-------------------------->		 68% of ITP	
Brown (1970)	<-----------------------|	 8%		 |---------------------->		 18%	
Ross (1972)	"Duration significantly related to ITP ($P < 0.001$)"						
Collin and others (1975)	61% (plastic cannulae) 47% (scalp vein needles)			|-----------------------> |---------------->			
Dinley (1976)	"Duration related to incidence and severity"						
Ferguson and others (1976)	(0% with heparin lock needles *in situ*) ---| (30% with heparin lock needles *in situ*)					 |---------->	
Stephen and others (1976)	"Duration of cannulation correlates with development of phlebitis in a linear fashion"						
Chamberland, Lyons and Brock (1977)	--| "most patients had inflammation"						
Eremin and Marshall (1977)	--------------------------------| ---| --|			10%	 48%	 80%	
Frazer, Eke and Laing (1977)	--------------------------------| --|			4.3%			 100%

cern.

PREDISPOSING FACTORS

The aetiology of ITP appears to be a combination of factors (Curry and Zallen, 1973).

Duration of infusion

The duration of infusion is such an important factor that undoubtedly it influences the effect of other factors (Ross, 1972). Nearly all investigators have reported that duration is significant (table III).

Site of infusion and size of vein

Data on the incidence of ITP related to the site of infusion are summarized in table IV. There is a tendency for smaller veins such as those on the dorsum of the hand to have a higher incidence of ITP. However, the series do not appear to be consistent and one may conclude that there is no clear evidence that any particular commonly used upper limb vein is more likely to develop ITP.

Few authors have commented on vein size. Those that do comment, agree that larger veins are to be preferred (Jones, 1957; Swanson and Aldrete, 1969; Sketch et al., 1972; Eremin and Marshall, 1977), but many patients prefer to have an i.v. infusion in the wrist or hand; for this is less restrictive than when the antecubital fossa is utilized.

Infection

Although any thrombus which develops around a cannula in a vein would seemingly provide an ideal site for bacterial multiplication, infection would not appear to be a major cause of ITP in the upper limb. Many of the studies cited in table V fail to show any correlation between infection and ITP. If the cause were bacterial, one might expect that antibiotic therapy would reduce the incidence of ITP, but there does not appear to be any study that demonstrates this. This does not exclude the possibility that ITP and infection may occur together, the infection being amenable to antibiotic therapy.

Types of solution infused

Most i.v. solutions have a low pH. Thus, solutions containing dextrose are usually of pH 3.4–5, while other solutions are around pH 5–6 (Tse and Lee, 1971). Reasons given for manufacturing such acid solutions are to prevent caramellization of dextrose (Ross, 1972), and to prevent reaction with glass containers during autoclaving. Despite the low pH, the buffering capacity of solutions is low.

Amino acid solutions are less irritant to veins when the pH is adjusted to 7.4 (Horvitz, Sachar and Elman, 1943). A number of workers have investi-

TABLE IV. *Site of infusion*

	Incidence at infusion site (%)					
Series and Year	Dorsum of hand	Dorsum of wrist	Forearm vein	Antecubital fossa	Cephalic vein	Other vein
Gjares (1957)	40	—	—	9	—	—
Eerola and Pontinen (1964)	41.8	—	—	26.1	—	—
Fonkalsrud, Murphy and Smith (1968)	18.1	—	23.4	—	—	—
Swanson and Aldrete (1969)	34.6	32.5	19.4	33.3	—	—
Brown (1970)	24	—	30	—	—	—
Eremin and Marshall (1977)	73	—	65	51	63	Subclavian 12
Skajaa and others (1961)	No significant differences					
Thomas, Evers and Racz (1970)	Venous complications lowest in the dorsum of the hand but not significant when time and cannulae considered					
Ross (1972)	More proximal veins (forearm) — higher incidence than distally					
Boon and others (1981)	No significant differences					

gated i.v. dextrose solutions. Vere, Sykes and Armitage (1960) conducted a blind, controlled trial of dextrose solutions sterilized by autoclaving or by filtration, and found that autoclaved solutions were acid and were associated with a significantly higher incidence of ITP than were filtered solutions of pH near neutrality. Buffering of solutions just before use has been demonstrated to reduce the incidence of ITP in both short- (Fonkalsrud et al., 1971) and longer-term infusions (Eremin and Marshall, 1977).

TABLE V. *Comments on infection*

Series	Comment
Jones (1957)	Argued against infection causing ITP, stating that "infection is never seen"
Cheney and Lincoln (1964)	Only 9.7% of cases with ITP grew pathogenic bacteria from equipment.
Kay and Roberts (1967)	One of 16 blood cultures positive. Two of 23 catheters had positive cultures.
Banks and others (1970)	45% of catheter tips grew bacteria, but only four of 118 patients had bacteraemia from same catheter/skin organism. No relation to duration, fluid or catheter type.
Collin and others (1975)	Teflon cannulae significantly associated with bacterial contamination and ITP.
Ferguson and others (1976)	Positive flush culture correlated with phlebitis when heparin lock needles used
Stephen and others (1976)	No instances of septicaemia despite a positive bacterial culture rate from cannulae of 48% of 130 patients.
Eremin and Marshall (1977)	22% of i.v. cannulae grew bacteria whether or not there was ITP or other infusion complication.
Archer and Fowler (1977)	No evidence that special skin preparation decreased incidence of ITP.

The low pH of i.v. fluid preparations has been implicated by other authors (Elfving and Saikku, 1966; Fonkalsrud, Murphy and Smith, 1968; Tse and Lee, 1971). Gritsch and Ballinger (1959) demonstrated in dogs that great damage to all layers of the vein wall was produced by acid solutions. Stephen and colleagues (1976) found that there was a significantly smaller incidence of ITP when normal saline alone was given, compared with other isotonic fluids or normal saline in combination with other fluids. Vascular endothelium is particularly sensitive to pH and in animal experiments platelet adherence to the damaged surface occurs with leucocyte infiltration and oedema (Eremin and Marshall, 1977). Maximal damage is seen near the tip of the cannula, but can spread proximally and cause intraluminal thrombosis. Prolonged infusion augments these pathological changes, but they are diminished by perfusion of solutions of neutral pH (Eremin and Marshall, 1977). Although alteration of pH towards neutrality may decrease venous irritation and ITP, Williams and Moravec (1967) reported that changing the pH of a solution can change the efficacy of some added drugs.

Hypertonic solutions also irritate veins (Gritsch and Ballinger, 1959). Since amino acid solutions and 50% dextrose can be tolerated only if given at a slow rate in large veins which have a high blood flow (Ravitch, 1969; Wilmore and Dudrick, 1969), they are usually infused through a central line.

Skajaa and co-workers (1961) found no difference in the incidence of ITP between 5% dextrose, physiological saline and blood. However, Dinley (1976) reported an extremely high incidence of venous reactions to blood transfusion. He commented that, as the vast majority of these transfusions were given from bottled blood, the plasticizers of polyvinylchloride bags can be excluded as a cause.

Particulate matter

Extraneous, mobile, undissolved substances in parenteral solutions constitute particulate matter. Examples are rubber, chemicals, glass, cellulose fibres and fungi (Garvan and Gunner, 1963).

Ryan, Rapp and De Luca, (1973) found that the use of a 0.45-μm filter reduced the incidence of phlebitis in patients receiving infusions for 72 h. De Luca and associates (1975) also found ITP to be significantly reduced in patients after operation when an in-line 0.45-μm filter was used. Turco and Davis (1971) and Davis and Turco (1973) have shown that every solution of every company tested contained particulate matter 5 μm and larger. Evans, Barker and Simone (1976) tested the effectiveness of a 5-μm filter in preventing phlebitis and found a significantly lower incidence in patients receiving filtered i.v. solutions.

Particulate irritation to the endothelium may result in inflammation of the vein. However, some investigators have failed to demonstrate the value of in-line filtration in reducing the incidence of ITP. Collin and colleagues (1973) and Chamberland, Lyons and Brock (1977) point out that the flow of infusate with 0.45-μm filters is impeded, filters need to be changed perhaps daily, and there is added expense. Collin and co-workers (1973) observed an incidence of phlebitis of 40% with filters and 47% without. Chamberland, Lyons and Brock (1977) found a 63%

incidence with filters, and 58% of patients without filters developed ITP.

In-line filtration, perhaps because of added cost, extra work and a restriction in the flow capacity of the infusion with small filters, is not commonly practised, although in theory it is a good idea, and there is some experimental evidence that it may be worthwhile.

Equipment

Needle or cannula. Skajaa and colleagues (1961) used three needle sizes, but did not observe differences in the incidence of ITP. Swanson and Aldrete (1969) found a significantly higher incidence with larger catheters than with 19-gauge needles. Curry and Zallen (1973) recommended the use of small-gauge (18–20) catheters and large diameter veins to reduce ITP. Thrombus formation is related to the size of device (Spanos and Hecker, 1976; Hecker, 1980), and so a build up of thrombus on a small cannula might be less likely to occlude the vessel. Even a partial occlusion may impede blood flow and a deleterious effect on the endothelium may be produced by the undiluted infusate (Hecker, 1980).

Winged Teflon cannulae may restrict movement in all planes, reduce irritation of the intima and reduce ITP.

Cannula material. Dinley (1976) showed that the incidence of venous reactions was related to the cannula material. He used cannulae of four types of material. Fluoroethylene propylene Teflon cannulae caused less reactions than tetrafluoroethylene Teflon. Polyvinylchloride and polyethylene cannulae were more irritant than either type of Teflon. Hecker (1980) measured thrombus formation associated with seven types of cannulae made of polyethylene, polypropylene and types of Teflon and found a significant difference of greater than two-fold in the amount of thrombus formed.

The roughness of the tubing or catheter tip may vary with the extrusion temperature during manufacture. Hecker and Edwards (1981) tested a polyvinylchloride resin tubing extruded at five different temperatures for thrombogenicity. Lower extrusion temperatures were associated with greater roughness and more thrombus formation.

Trauma at venepuncture. James (1954) suggested that greater experience in performing venepuncture decreases the incidence of ITP. Watt (1977) was concerned that the trauma of insertion provides bacterial access to the circulation. Eremin and Marshall (1977) suggested that trauma is more likely to occur to smaller veins at the time of insertion of the cannula and they felt that plastic cannulae inserted through an i.v. needle may be associated with less trauma to the vein than the plastic cannulae inserted as a sheath around the venepuncture needle. They found that complications were highest with the latter type of cannula and, also, highest in small veins. In other studies, Jones (1957) found that venepuncture was not a significant factor and McNair and Dudley (1959) regarded it as a minor factor. Hästbacka and associates (1965) reported that the incidence of ITP did not seem to be any higher when a haematoma formed as a result of venepuncture.

Infusion set. Handfield-Jones and Lewis (1952) obtained a reduction of 50% in the frequency of ITP when they used plastic instead of rubber sets. This finding was confirmed by the (British) Medical Research Council (1957). Rubber tubing is of historic interest, but more recently Skajaa and colleagues (1961) found no difference between two types of plastic infusion sets.

Rate of flow

Hessov and Bojsen-Møller (1976) suggest that the rate of infusion is important, with it being advantageous to give irritant solutions quickly. Ross (1972) could find no studies which compared infusion flow rates with the incidence of phlebitis. In her series, the mean infusion rate ranged from 59 to 325 ml per hour. She felt that a significant correlation between slower end-infusion rates and the incidence of phlebitis may indicate that injury to the vein by an irritating solution is apt to occur with slow infusions. It is possible that the lower end-infusion rates were the result of venoconstriction induced by the infusion and that this may be an early indication of the likely development of ITP. Evans, Barker and Simone (1976) found no correlation between flow rate and the incidence of phlebitis.

Age

Aldman and Garsten (1960), Hästbacka and colleagues (1965), Fonkalsrud, Murphy and Smith (1968), Swanson and Aldrete (1969), Dinley (1976) and Archer and Fowler (1977) were unable to show a consistent trend between age and the incidence of ITP. Hastbacka and co-workers (1965) showed a tendency for the incidence to be lower in younger age groups, but Skajaa and colleagues (1961) found it was the younger patients who tended to have the higher incidence.

Sex

Hästbacka and co-workers (1965) noted that the frequency of phlebitis in females was about twice as high as in males after thiopentone injection: after pethidine injection no difference was seen. Archer and Fowler (1977) reported that the female incidence was twice that of males. No sex-related differences were detected by Aldman and Garsten (1960), Skajaa and associates (1961) or Dinley (1976).

Administered drugs

Benzodiazepines. Wyant and Studney (1970) observed that phlebitis was not uncommon when diazepam was administered to induce anaesthesia, but the incidence of venous reactions after i.v. benzodiazepines varies in different studies. This may be attributable to solvents, size of veins, method of injection and follow up. Hegarty and Dundee (1977) reported that age may also be important. A time-related increase in frequency during the first days after injection was noted by Siebke, Ellertsen and Lind (1976), Hegarty and Dundee (1977) and Mikkelsen and colleagues (1980). Langdon, Harlan and Bailey (1973) observed an ITP incidence of only 3.5% after i.v. diazepam, whereas Hegarty and Dundee (1977) found an incidence of 39%. Mikkelsen and co-workers (1980) reported an incidence of about 14% after both diazepam and flunitrazepam, whereas Hegarty and Dundee (1977) observed only a 5% incidence with nitrazepam. The solvent used in the preparation of the parenteral benzodiazepines such as flunitrazepam and diazepam is commonly propylene glycol, which may play a significant role in the aetiology. When oxazepam dissolved in propylene glycol was injected i.v. to dogs (Alván et al.,1974), haemolysis and ITP were observed after rapid infusion and were shown to be caused by the properties of the vehicle. Mattila, Rossi and Ruoppi (1981) showed a reduction of venous sequelae of i.v. diazepam when a fat emulsion was used as the solvent.

Barbiturates and other anaesthetic agents. Barbiturates have been implicated as aetiological agents by Kivalo and Tammisto (1959), Eerola and Pöntinen (1964), Hästbacka and colleagues (1965), Hewitt and co-workers (1966), O'Donnell, Hewitt and Dundee (1969), Carson and colleagues (1972) and Jamieson. Desjardins and Caron (1972). Hästbacka and associates (1965) found that complications occurred more often after the injection of 5% sodium thiopentone than after 2.5% solution.

Hewitt and colleagues (1966) reported that the injection of propanidid was associated with an increased incidence of ITP. O'Donnell, Hewitt and Dundee (1969) noted that greater dilution of propanidid significantly decreased the incidence of venous sequelae. Carson and colleagues (1972) reported that one of the major drawbacks in the development of non-barbiturate i.v. anaesthetic agents has been the high incidence of local venous thrombosis. They cited hydroxydione as an example. They found that the newer steroid Althesin had a lower incidence than either 5% propanidid or 5% thiopentone solutions. There was no difference between the effects of Althesin, 2.5% thiopentone and 1.0% methohexitone.

Etomidate causes such severe pain to some patients on injection that its value for induction is limited (Kenny, 1981). Pain on injection was avoided by Lees and colleagues (1981) who used etomidate and fentanyl only as an infusion for maintenance of anaesthesia, but they reported a 22% incidence of thrombosis or ITP compared with a 10% incidence in control patients in whom halothane was the maintenance agent.

Boon and co-workers (1981), in a study of 16 drugs commonly used in anaesthetic practice, concluded that "the injection of anaesthetic agents into an intravenous line does not result in an increased incidence of local thrombosis or phlebitis in the 48 hour period after surgery". However, the incidence of ITP in their series was 36%.

Antibiotics. "Antibiotics may also be associated with phlebitis and other routes of administration should be considered" (Stephen et al., 1976).

Cephalosporin antibiotics have been associated with a high incidence of ITP (Perkins and Saslaw, 1966; Storey, 1971; Bran, Levison and Kay, 1972; Lane, Taggart and Iles, 1972; Inagaki and Bodey, 1973). Siebert and colleagues (1976) studied the incidence and severity of ITP associated with cefamandole, cephapirin and cephalothin. The incidence was similar for each drug, but ITP was significantly more severe with cephalothin than the other agents. These results are in agreement with the findings of Lane, Taggart and Iles (1972) and Inagaki and Bodey (1973).

Tetracyclines added to i.v. infusions had no effect on the complication rate in Eremin and Marshall's (1977) study, but increased the risk of phlebitis in Kay and Roberts' (1967) series. Crystalline penicillin and ampicillin had no effect on the incidence when added to Eremin and Marshall's (1977) infusions. Addition of ampicillin to infusions reduced the incidence of ITP in Brown's (1970) study, but Thomas, Evers and Racz (1970) gained a strong clinical impression that the onset of phlebitis was hastened by ampicillin.

Other drugs. Kay and Roberts (1967), Thomas, Evers and Racz (1970) and Stephen and colleagues (1976) all found that potassium chloride added to an infusion increased the risk of phlebitis, but Eremin and Marshall (1977) found no change in risk. Nordell, Mogensen and Nyquist (1972) found a correlation between i.v. lignocaine infusions and ITP. Hästbacka and co-workers (1965) reported that injection of undiluted pethidine increased the incidence of ITP by about one-third. A histamine-like reaction along the course of the vein followed pethidine administration in 25% of cases. The incidence of this reaction showed a correlation with subsequent ITP, contrary to the situation with barbiturates, with which ITP does not appear to be related to an acute venous response.

Other factors

A history of previous phlebitis or allergy have been suggested as possible causative factors, but no correlation between these factors and ITP has been found (Aldman and Garsten, 1960; Hästback et al., 1965). Brown (1970) commented that, if a needle is left in a vein without an infusion, the incidence of ITP is very low, even after 72 h. Obesity does not seem to be a factor (Hastbacka et al., 1965).

Michaels and Reubner (1953) suggested that contaminated infusion fluid may give rise to phlebitis, but this should be considered under the heading of suppurative thrombophlebitis discussed earlier.

Although cardiovascular disease did not appear to predispose to ITP, Hastbacka and colleagues (1965) found an incidence of 53% in those patients with a circulation time of greater than 19 s, compared with 35% with a circulation time of less than 15 s. A further analysis of those whose circulation time exceeded 25 s showed a phlebitis incidence of 88%. No other studies of a similar nature appear to have been reported.

TREATMENT OF INFUSION THROMBOPHLEBITIS

Removal of the i.v. device at the earliest opportunity is the primary treatment. Since ITP is a sterile inflammation, the use of anti-inflammatory agents is indicated. Oxyphenbutazone has been used to treat ITP. Archer and Fowler (1977) point out that phenylbutazone and oxyphenbutazone became accepted as therapeutic agents without a solitary satisfactory double-blind controlled study. They agree that their study is also flawed, for when studying the efficacy of oxyphenbutazone, the treatment group were initially more affected by ITP than the controls with regard to pain, area of erythema and length of indurated vein. Despite bias against the treatment, they found oxyphenbutazone effective in rapidly relieving pain and tenderness. A 70% improvement in pain when compared with initial severity occurred within 4 days, compared with a 43% improvement in the placebo group. A parallel improvement in tenderness was also noted. The area of erythema showed marked resolution in the same period. They concluded that the reduction in pain occurred with resolution of inflammation and was not merely the result of an analgesic effect.

Application of other anti-inflammatory agents such as hydrocortisone cream is common and analgesics are given for symptomatic relief. Hirudoid, a heparinoid preparation has been applied, but Hästbacka and colleagues (1965) stated that the value of this treatment seems questionable. In their series, the symptoms of ITP sometimes persisted for months, the longest for 7 months after infusion.

ITP is a painful condition and therefore analgesics are indicated. Drugs such as aspirin may inhibit pathological changes associated with prostaglandins (see next section).

PREVENTION

The surest way to prevent ITP is to avoid setting up or continuing an infusion unnecessarily. When prolonged i.v. therapy is required, it is recommended that the site of infusion be changed every 24 or 48 h where practical, as duration of infusion is an important factor. This is not always practical.

Another way to reduce the incidence of ITP is by adding certain drugs to the infusion solution. Anderson (1951) showed a significant delay in the development of ITP with the addition of heparin. Daniell (1973) added heparin 1000 i.u./litre 5% Dextrose B.P. and reduced the incidence of ITP in a double-blind controlled study. Other studies have also demonstrated a reduction in thrombosis when heparin is given (Martin, 1944; Erwin, Strickler and Rice, 1953; Wessler and Rogers, 1956; Hohn 1966; Sketch et al., 1972; Stephen et al., 1976) and Eremin and Marshall (1977) also commented that heparin appeared to reduce the incidence, although their numbers were small. A number of studies utilizing different types of catheter (McNair and Dudley, 1959; Martin, 1965; Roy, Wilkinson and

Bayliss, 1967; Walters, Stanger and Rotem, 1972) have not demonstrated a significant effect. Pussell and Pitney (1972) observed that the incidence of thrombosis at the i.v. cannula site was approximately 75% in patients who were receiving anticoagulant drugs (heparin or heparin followed by warfarin) and in those who were not, in a study of patients following myocardial infarction. Polok (1956) advocated the use of hydrocortisone and McNair and Dudley (1959) reported that it definitely reduced the incidence and severity of ITP. Clark, Polak and Hajnal (1960) showed that the incidence decreased when hydrocortisone was added to the infusion solution. Schafermeyer (1974) recommended that heparin 5 mg and hydrocortisone 1 mg be added to each litre of i.v. fluid when cephalothin, gentamicin, kanamycin and potassium salts are to be administered.

A different regimen was adopted by Woodhouse (1979), who used a local heparin and hydrocortisone cream over the infusion site. He found that 15 of 49 control patients, compared with only eight of 48 treated patients, developed ITP. Patients in the treatment group took longer to develop ITP (66.4 h *cf* 47.4 h). Eerola and Pontinen (1964) investigated the prophylactic effect of two anticoagulant ointments, Thrombosol forte (containing heparin) and Hirudoid (containing a heparinoid). Following infusions for an average duration of 4–5 h, 21.4% of the arms with Hirudoid or Thrombosol forte treatment showed signs of ITP. The corresponding figure in the untreated group was 25.9%. The duration of ITP, when it developed, was shorter in the treatment group.

Prostaglandins and related compounds are involved in the processes of haemostasis and thrombosis. Aspirin, indomethacin and phenylbutazone inhibit prostaglandin synthesis. Thromboxane A_2, which is synthesized by platelets and other cells, induces platelet aggregation, whereas PGI_2, which is synthesized by vascular wall cells, inhibits platelet aggregation (Moncada et al., 1976). Aspirin inhibits the release reaction by acetylating platelet cyclooxygenase and so inhibits the synthesis of prostaglandins and thromboxane A_2 (Roth and Majerus, 1975). Aspirin inhibits PGI_2 synthesis by the vessel wall, which could be potentially thrombogenic. The dose of aspirin required for different effects is different (Kelton et al., 1978), so when aspirin is used as an antithrombogenic agent, the doses used may inhibit platelet prostaglandin synthesis without affecting PGI_2 formation by the vessel wall. It is now thought that the antipyretic, analgesic and anti-inflammatory actions of aspirin-like drugs are mediated via inhibition of prostaglandin biosynthesis, but a place for aspirin in the prophylaxis of ITP is not established.

There is little evidence that antibiotics, either by infusion or applied locally, influence the incidence of ITP (Norden, 1969; Zinner et al., 1969; Evans, Barker and Simone 1976), except that ampicillin appeared to lower the incidence in Brown's (1970) series.

The use of buffered solutions lowers the risk of phlebitis. Fonkalsrud, Murphy and Smith (1968) showed that a significant reduction in endothelial injury occurred when the infusion solution was buffered to pH 7.4. Approximately 15 mmol of sodium bicarbonate is sufficient to buffer 1 litre of 5% dextrose B.P. solution.

It is common observation that infusion rates often slow down after some hours. One likely explanation is increased resistance brought about by local venoconstriction at the site of infusion. This is caused by irritation induced by infused solutions (Lewis and Hecker, 1984) and this will decrease blood flow past the cannula tip, reducing dilution of infusate by the blood. Further slowing of the drip rate may occur with continued irritation, and relative stasis could encourage thrombus formation. Increased exposure of endothelium to infusate might lead to swelling of endothelial cells and development of oedema.

CONCLUSION

The lack of a universally applied clinical definition of ITP makes a valid comparison of incidence and severity well nigh impossible. A multitude of factors appears to be involved in the development of this condition. Of those factors, the more important are duration, drugs administered and solutions infused. There is little detailed knowledge of the histopathology, although there is increasing awareness of the involvement of prostaglandins and possibly leukotrienes in its pathophysiology.

Prophylaxis is often inadequate, despite recommendations for the neutralization of acid solutions and the limiting of the duration of infusions. This is reflected in the continuing high incidence, with a significant morbidity complicating i.v. therapy. Until this iatrogenic condition is studied under more controlled conditions, we are not likely to understand the pathophysiological details upon which effective prophylaxis and management should be based.

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Br. J. Anaesth. (1985), **57**, 234–242

CORRESPONDENCE

COMPARISON OF PROPOFOL IN EMULSION WITH ALTHESIN FOR INDUCTION OF ANAESTHESIA

Sir,—The withdrawal from the market of Althesin and propanidid has reduced significantly the available choice of i.v. induction agents in the U.K. Propofol (2, 6 diisopropylphenol), previously formulated in Cremophor EL, is now produced in an emulsion to exclude Cremophor-related reactions and decrease the incidence of pain on injection. The two formulations have similar anaesthetic properties, although a small decrease in potency has been observed with the emulsion (Cummings et al., 1984; Glen and Hunter, 1984). We have compared propofol in emulsion with Althesin during the induction of anaesthesia.

Forty unpremedicated patients, ASA grade 1, aged 18–65 yr, undergoing minor surgical procedures, were studied. The patients were allocated randomly to receive either 1% propofol (20 patients) in an oil in water emulsion 2.5 mg kg^{-1} over 20–30 s or Althesin 0.05 ml kg^{-1} given at a rate of approximately 1 ml per 20 s (manufacturer's data sheet). Injections were made via a 21-gauge indwelling needle in the dorsum of the hand. One investigator administered the test drug while another, who was unaware of which drug was being given, recorded the findings in all 40 patients; this was achieved by shielding the test drugs with a hand towel during injection. Apart from oxygen, no other drug was given for 2 min from the start of injection. Thereafter, nitrous oxide and halothane were introduced. The following were recorded: success of induction (loss of eyelash reflex and lack of response to application of facemask); induction time (time to loss of eyelash reflex or time to application of facemask without response), systolic and diastolic arterial pressures and heart rate (Dinamap, Critikon) before, and at 2 and 3 min after, the start of injection, occurrence and duration of apnoea; excitatory movements; reported sensations at the injection site; an overall assessment (good, adequate or poor). Results were analysed by Student's *t* test or Fisher's exact test where appropriate.

There were no differences between the groups with respect to age, weight or sex. Induction times were shorter with propofol (mean 45 s, range 35–65) than Althesin (mean 73 s, range 50–120). Apnoea occurred in 10 patients receiving propofol (mean 35 s, range 20–55) and in one patient receiving Althesin ($P < 0.01$). Excitatory movements occurred in three patients receiving propofol and in six patients receiving Althesin (ns). Pain on injection occurred in four patients with propofol (one severe) but did not occur in the Althesin group. At 3 min from the start of injection, systolic and diastolic arterial pressures decreased to 81% and 80%, respectively, of the pre-induction values with propofol, and to 92% and 95% with Althesin (fig. 1). The differences between the two groups were significant ($P < 0.01$) for both systolic and diastolic pressures. Over the same period, heart rate increased by 21% of the pre-induction value with Althesin, but did not change with propofol ($P < 0.01$). Induction was assessed as good or adequate in all patients receiving propofol, but in only 16 of the patients receiving Althesin.

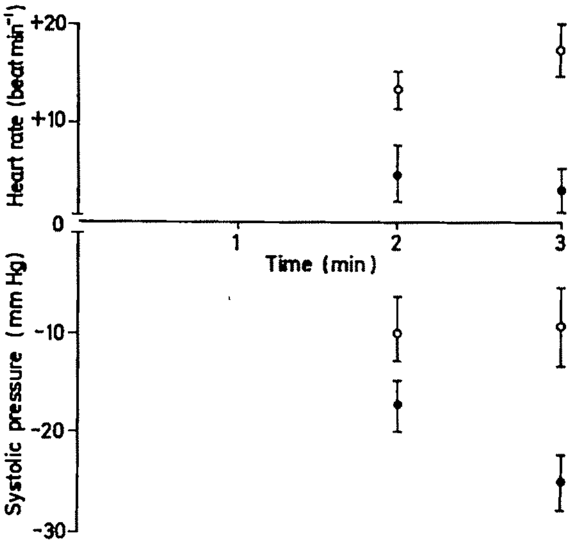

FIG 1. Mean (± SEM) changes in systolic arterial pressure (mm Hg) and heart rate (beat min^{-1}) from baseline associated with i.v injection of propofol 2.5 mg kg^{-1} over 20–30 s (●), or Althesin 0.05 ml kg^{-1} (○) given at a rate of 1 ml per 20 s.

We conclude that propofol in emulsion compares well with Althesin for the induction of anaesthesia. However, propofol caused a greater decrease in arterial pressure with less change in heart rate than Althesin, and may cause apnoea and pain at the injection site.

G. C. CUMMINGS
A. A. SPENCE
Glasgow

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INFUSION RATES FOR I.V. ANAESTHESIA

Sir,—The study of Wright and colleagues (1984) demonstrated an important between-patient variation in dose requirement for both intermittent i.v and continuous infusion anaesthesia, as well as the limitations of mean values when applied to the requirements of the general patient population. The range of dosage was probably reduced by opioid premedication but, nevertheless, this skew distribution persisted.

A similar study has been carried out with methohexitone, initially using intermittent increments following an induction dose of 1.6 mg kg^{-1} and later, based on these findings, with infusion

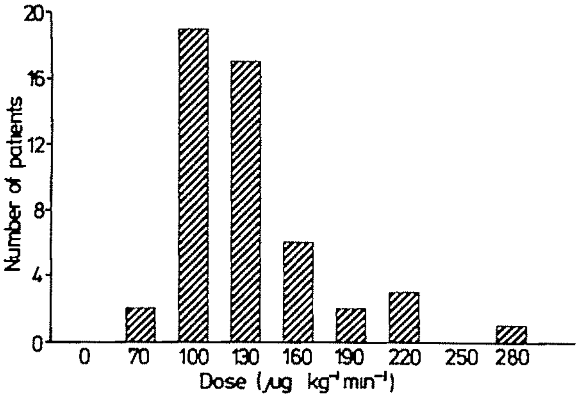

FIG 1 Distribution of methohexitone requirements at 45 min in 50 unpremedicated patients.

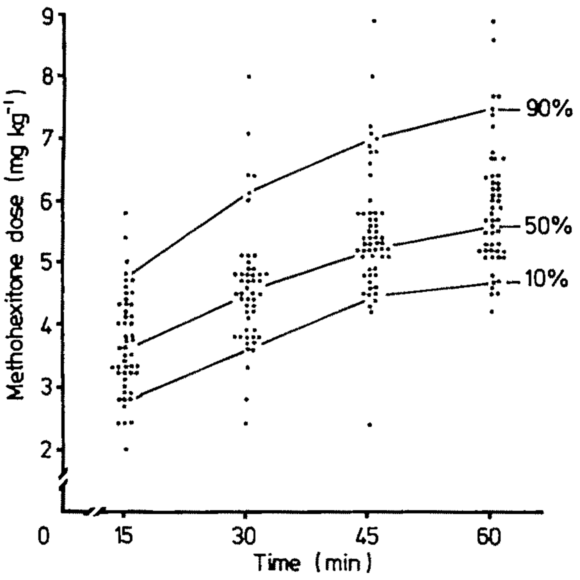

FIG 2. Distribution of requirements at 15-min intervals.

supplemented by small increments, as required. The distribution of total 45-min dose requirements (intermittent injection) in 50 patients is shown in figure 1, while figure 2 shows individual dose requirements at 15-min intervals. $\log_e$ transformation normalized this skew distribution and the mean value of the transformed data (154 μg kg^{-1} min^{-1}) was the basis for an infusion technique. Given with 67% nitrous oxide in oxygen to patients undergoing body surface operations with spontaneous ventilation, this dose produced effective anaesthesia in 90% of patients. An infusion rate of 192 μg kg^{-1} min^{-1} was required to ensure effective anaesthesia in all patients.

These findings again show the biological variation in requirements of hypnotic drugs. Together with those of Wright and his colleagues (1984), they show the high predictive value of the intermittent injection technique for infusion rates. In addition, they show the limitations of average rates as means of providing anaesthesia in 100% of patients.

J W. DUNDEE
T. J. McMURRAY
Belfast

REFERENCE

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HUNTINGTON'S CHOREA
A ROLE FOR THE NEWER ANAESTHETIC AGENTS

Sir,—The provision of anaesthesia for patients suffering from Huntington's chorea has posed problems for the anaesthetist over the past few years. Reports suggesting prolonged clinical responses to both thiopentone (Davies, 1966; Blanloeil, Bigot and Dixneuf, 1982) and suxamethonium (Gualandi and Bonfanti, 1968) have been published in addition to the observations of abnormal plasma cholinesterase variants in these patients (Whittaker, 1980) Although standard anaesthetic regimens using opioids and non-depolarizing myoneural blocking drugs (with and without halothane supplementation) have been used successfully (Farina and Rauscher, 1977; Browne and Cross, 1981), another report suggests the sole use of nitrous oxide, oxygen and a volatile agent (Lamont, 1979). The absolute requirement of rapid, dependable recovery from anaesthesia where the risk of a compromised airway is present, in oro–facial or ENT surgery, or the presence of co-existing ischaemic heart disease or chronic lung disease, makes the latter technique less than ideal The recent development of short-acting i.v. anaesthetic agents suggests a new approach to these problems.

A 58-yr old man (70 kg), with established Huntington's chorea, presented for bilateral antral washout and nasal polypectomy. Although his chorea was moderately controlled by haloperidol 2.5 mg 12 hourly and tetrabenazine 25 mg, 8 hourly, he was markedly dysphasic and emotionally labile. He suffered from occasional angina pectoris and chronic bronchitis, placing him in ASA category III.

Following premedication with diazepam 10 mg orally, anaesthesia was induced using alfentanil 0 5 mg followed by Althesin 3.5 ml (diluted to double the volume with saline) Intubation of the trachea was achieved easily in 90 s following atracurium 25 mg. A transient decrease in arterial pressure from a preoperative value of 140/70 mm Hg to 80/50 mm Hg followed induction, but this increased to 110/60 mm Hg by the start of surgery. Anaesthesia was maintained with nitrous oxide in oxygen by IPPV, aliquots of Althesin 0.5 ml and a single incremental dose of alfentanil 0 15 mg. Surgery was uneventful, lasting 30 min, during which the patient's arterial pressure continued to increase to a value of 160/100 mm Hg, the heart rate remaining below 85 beat min^{-1}.

Whilst a good "train-of-four" response was elicited immediately on ending surgery, and spontaneous respiration with an active cough reflex established on cessation of IPPV, the patient remained drowsy for a few minutes. Neostigmine 1.25 mg with atropine 0.6 mg and naloxone 0.2 mg were given as a precautionary measure to ensure full recovery. Further recovery in theatre, recovery room and on the ward was smooth and uneventful, with the patient remaining comfortable, protecting his airway and talking to the nursing staff.

The short delay in awakening following the moderately small doses of the anaesthetic agents is not entirely unexpected in the light of previous reports, albeit using different agents. Whether this was an intrinsic sensitivity as a result of the neurohumoral abnormalities found in Huntington's chorea or the result of interaction with the patient's medication of haloperidol and tetrabenazine, remains unclear. However, recovery was safely sustained, and we suggest that the judicious use of these short-acting i.v. agents may provide the means for successful anaesthesia in patients with Huntington's chorea, without the use of volatile agents.

M. K. JOHNSON
N M. HEGGIE
Sunderland

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MANAGEMENT OF BLUNT TRAUMA TO THE CERVICAL PORTION OF THE TRACHEA

Sir,—The case report by Dash and Gode (1983) has prompted us to suggest an alternative management and to describe our approach to such injuries. Frequently, laryngotracheal injuries are either overlooked or are diagnosed only after a significant delay. In fact, a 31% frequency of delay in establishing the diagnosis in a series of patients with laryngeal injuries has been reported (Thompson and Jacobs, 1983) Therefore, a high index of suspicion must accompany the initial evaluation of all patients with blunt or penetrating trauma to the neck, particularly when symptoms of hoarseness, neck swelling or haemoptysis are present. Laryngotracheal injury can result in the insidious onset of subcutaneous emphysema some hours after injury, as described by Dash and Gode. When definitive surgical repair of the tracheal inlet is delayed, the resultant recovery is less than ideal (Brandenberg, 1979; LeMay, 1971; Flood and Astley, 1982).

Early diagnosis of injury to the laryngotrachea is best accomplished by direct laryngoscopy and bronchoscopy. In this era of flexible nasopharyngoscopes and bronchoscopes, the airway can be inspected under local anaesthesia at the time of admission without an appreciable increase in morbidity or risk. Not only is early diagnosis of cervical trauma mandatory for optimal surgical repair, it also has the potential for avoiding the problem of unsatisfactory endotracheal intubation encountered by Dash and Gode. Laryngoscopy or bronchoscopy, or both, carried out before intubation is attempted helps to localize and define the extent of injury and might encourage one of several alternative methods of endotracheal tube placement, so that the distal tip of the tube will lie distal to the cervical tracheal tear.

If a rigid ventilating bronchoscope is used with general or topical anaesthesia in a patient with cervical trauma, a tracheotomy can be performed with good control of the airway. If endotracheal intubation is required, a woven stylette or Fogarty arterial embolectomy catheter (Edwards Laboratories, Inc., P.O. Box 11150, Santa Ana, Ca.92711, U.S.A.) can be passed through the bronchoscope to act as a guide during immediate laryngoscopy by the anaesthetist. For this procedure, we gently inflate the balloon tip to hold the catheter in the right main-stem bronchus as the bronchoscope is withdrawn. Under direct vision, we insert forceps, clasp the catheter at the laryngeal inlet, and cut the inflating luer-lock from the proximal end, allowing the cuff to deflate. We then quickly but gently pass a cuffed endotracheal tube of small internal diameter (MLT Tracheal Tube, NCC Division, Mallinckrodt, Inc., 230 Dix Avenue, Glens Falls, N.Y. 12801, U.S.A.) over the guide so that it passes the lesion and allows the usual placement of the endotracheal tube and ventilation. Rogers and Benumof (1983) have suggested placing the endotracheal tube under direct flexible laryngoscopic examination, which also allows visualization of the tracheal or laryngeal injury and safe passage of the endotracheal tube.

We believe that careful endoscopic examination of the laryngotrachea before the endotracheal tube is placed in a patient with cervical trauma will ensure an adequate airway with less morbidity and risk, ensure early diagnosis of laryngotracheal injury, and thus ensure that the surgical result will be more satisfactory.

J. N. THOMPSON
D. B. WEEKS
Winston-Salem, N Carolina

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Thompson, J. N., and Jacobs, J. R. (eds) (1983). External injuries of the larynx; in *Maxillofacial Trauma: An International Perspective*, p.165. New York: Prager Publishers.

Sir,—I read with interest your recent case report of an injury caused by blunt trauma to the cervical portion of the trachea (Dash and Gode, 1983). While I would agree with the authors that accurate diagnosis is important, and that gross surgical emphysema may make this very difficult, the difficulties encountered do not suggest that their approach was entirely logical. The value of an alternative method is illustrated by a recent case.

A previously fit 44-year-old man presented to the Casualty Department after having water-skied into the side of a stationary boat. The presence of surgical emphysema in the neck and upper chest, pneumomediastinum without pneumothorax, and mild haemoptysis led us to suspect the possibility of a tracheal rupture. He had also sustained a forearm fracture and a closed eye injury.

He was prepared for theatre urgently. A fibreoptic bronchoscope was passed orally under diazepam sedation and topical lignocaine spray and the tracheal tear was easily visualized 2 cm above the carina. A Portex endotracheal tube (7 mm) was passed over the bronchoscope into the left main bronchus and anaesthesia was induced using thiopentone and suxamethonium. The tracheal tear was sutured, with surgical access through a right thoracotomy. When the repair was complete the tube was pulled back into the trachea above the injury. Since testing at the end of the operation showed the repair to be airtight up to pressures of 60 cm H_2O, neuromuscular blockade was reversed and the trachea extubated immediately. After 12 h in the ITU he was discharged to the ward where he made an uneventful recovery and was discharged home on the 10th day.

Swelling of the neck as a result of surgical emphysema often makes estimation of the exact level of the rupture extremely difficult. Closed rupture can occur at any point in the tracheobronchial tree, and the site of the rupture can affect management dramatically. Ruptures occurring in the lower trachea are approached via a right thoracotomy (Olson and Johnson, 1971; Urschel and Razzuk, 1973). For safe anaesthesia in these circumstances it is necessary to pass the cuff of the endotracheal tube past the rupture to allow intermittent positive pressure ventilation once the chest is opened. This can only be done with certainty by railroading the tube over the bronchoscope under direct vision. This technique should also minimize the possibility of failed intubation because of obstruction caused by the disrupted trachea, as happened in the reported case.

If the diagnosis of tracheal rupture is suspected, bronchoscopy before intubation should be mandatory in order to assess correct management. This may be performed either before anaesthesia or following an inhalation induction.

G. D. PRINCE
Newcastle-upon-Tyne

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Urschel, H. C., and Razzuk, M. A. (1973). Management of acute traumatic injuries of tracheobronchial tree. *Surg. Gynaecol. Obstet.*, **136**, 113.

Sir,—We would like to thank Dr Prince for showing a keen interest in our clinical report. Before commenting on the alternative method, we would like to clarify his misinterpretation of the anaesthetic management. In the discussion we have stressed the problem of intubation and admitted "intubation of the trachea would have been uneventful, had we refrained from manipulating the endotracheal tube to overcome the resistance." In the concluding paragraph we emphasized the danger of "manipulation of the endotracheal tube in order to overcome the resistance". His mention of "failed intubation" was never encountered during the anaesthetic management.

Anaesthesia is an ever changing specialty, as a result of introduction of new technology. We agree with the suggested alternative technique of Dr Prince—the use of fibreoptic bronchoscope for visualization of the tracheal tear and rail-roading of the endotracheal tube. However, this method of intubation requires the availability of suitable equipment. Although the method described by Dr Prince is useful in the hands of an expert, coughing has to be carefully avoided during bronchoscopy as it may lead to exacerbation of air leak through the tracheal tear, resulting in pneumothorax or pneumomediastinum.

Furthermore, only a few centres in the developing world possess the fibreoptic bronchoscope. In such situations the technique described in our article is safe and simple.

H. H. DASH
G. R. GODE
New Delhi

SELECTIVE CONTRALATERAL BRONCHIAL INTUBATION IN CHILDREN WITH PNEUMOTHORAX OR BRONCHOPLEURAL FISTULA

Sir.—In their paper Baraka, Dajani and Maktabi (1983) have described in detail the management of anaesthesia in two children. One child had a tension pneumothorax on the left side, following rupture of a lung abscess. The preoperative x-ray clearly shows a tension pneumothorax on the left side, with depression of the left dome of diaphragm, a horizontal fluid level at the base, and very marked deviation of the mediastinum to the right. The mediastinal deviation to the right is so marked that the whole of the cardiac shadow is on the right side of midline.

The second child had empyema on the right side, following right lobar pneumonia. The preoperative x-ray shows a horizontal fluid level on the right side of the chest with a slight shift of mediastinum to the left. With a horizontal fluid level the diagnosis in this patient is also a pneumothorax on right side with empyema.

In both these patients, the broncho-pleural communication is beyond suspicion, and in both there is a fluid level at the base. Tension pneumothorax is the main factor in the first patient, while highly infected empyema fluid with a communication with the tracheo-bronchial tree is the main feature in the second patient.

The authors have described the management of both patients, the main features of which can be summarized as follows:
(1) Supine position for induction.
(2) Pre-oxygenation.
(3) Induction with thiopentone and suxamethonium followed by apnoea.
(4) Endobronchial intubation.

After establishing, or even after suspecting, the existence of tension pneumothorax, I feel that the management described by the authors was not only not correct, but positively fraught with danger.

Before any induction of anaesthesia, it was absolutely essential to introduce an indwelling underwater drain to the first patient, under topical analgesia with the patient sitting up and not supine. The relief of the tension pneumothorax with correction of the shift of the mediastinum was the only way to restore the patient's respiratory and circulatory status. Induction, as described, could have resulted in increasing the tension pneumothorax, and sudden cardiovascular collapse.

In the second patient there was a real danger, before endobronchial intubation of the contralateral side, of producing a tension pneumothorax and of soiling the healthy lung, unless an underwater drain (preferably two tubes, one for the air and the other for the empyema fluid at the base) was inserted. A major spill over onto the healthy side did occur, as shown by the post-operative x-ray of the second patient.

Whatever the merits of the endobronchial intubation, it seems to me that, in the two patients mentioned, the management as described was inappropriate and, if repeated, the next patient may not be so lucky.

It should be emphasized that presence of pneumothorax and pneumothorax with empyema makes it absolutely mandatory to put in underwater drains under topical analgesia, before any intubation, endobronchial or otherwise, is undertaken.

Y. G BHOJRAJ
Bombay

REFERENCE

Baraka, A., Dajani, A., and Maktabi, M. (1983). Selective contralateral bronchial intubation in children with pneumothorax or bronchopleural fistula. *Br. J. Anaesth* , 55, 901.

Sir,—Thank you for referring the letter of Dr Bhojraj concerning our report "Selective Contralateral Bronchial Intubation in Children with Pneumothorax or Bronchopleural Fistula". I agree with Dr Bhojraj that the merits of bronchial intubation should not deviate us from the proper anaesthetic management of such patients As a matter of fact, the aim of our publication was to describe the technique of selective contralateral bronchial intubation in children having empyema or pneumothorax, and to report that massive transbronchial spread of empyema can occur despite selective bronchial intubation.

Also, I agree with Dr Bhojraj that preoperative underwater seal drainage under local anaesthesia is advisable in patients with pneumothorax or empyema. This is our practice in adults. However, general anaesthesia may be advised in children. In the paediatric age group, we recommended in our report the induction of general anaesthesia with a head-up tilt, while the child was breathing spontaneously an inhalation anaesthetic, or by using a "crash" induction of anaesthesia as described in our report In all cases of empyema or tension pneumothorax, we must presume the presence of a bronchopleural fistula and controlled ventilation should be commenced only after ensuring contralateral bronchial intubation.

A. BARAKA
Beirut

EXTRADURAL DROPERIDOL POTENTIATES EXTRADURAL OPIOIDS

Sir,—The extradural administration of opioids has been effective in the treatment of pain. Nevertheless, especially in the case of terminal cancer, supplementary medication may be necessary.

It has been demonstrated that parenterally administered opioids may be potentiated by means of dopamine receptor blocking agents, such as neuroleptics (Tulunay, Ischiro and Takemori, 1976). Furthermore, a descending and an independent dopaminergic system has been discovered (Hokfelt, Phillipson and Goldstein, 1979; Karoum et al., 1980). In 1980, Kim and Stoelting showed that the simultaneous instillation of morphine and droperidol in rats prolonged the mean duration of action of morphine alone by approximately 40%. Neuroleptic agents may increase the analgesic effect of opioids by impairing the dopaminergic impulses at a segmental level of the spinal cord.

Inspired by this study, we attempted instillation of droperidol in order to potentiate extradural opiates in two patients suffering from intractable chronic pain from malignant disease. We chose droperidol on account of the previous results, the suitable concentration, identical pH values when compared with morphine, and the lack of preservatives in the solution.

In one patient, a 60-year-old female with cancer of the urinary bladder, the mean daily dose of extradural opioid had been increased from morphine 18 mg to a total of morphine 30 mg, without producing adequate analgesia. Supplementary medication with extradural droperidol 2.5 mg before the instillation of the morphine twice daily produced satisfactory analgesia. The patient experienced a minor degree of sedation, which she easily accepted. The dose of morphine remained constant for more than 2 months. The other patient, a 70-year-old female with terminal breast cancer, was treated with extradural buprenorphine 0.6 mg three times daily. Adequate analgesia was not achieved until droperidol 2.5 mg was added twice a day previous to instillation of the opioid. No unwanted side effects were observed and the dose of buprenorphine remained constant until the patient died 1 month later.

We find our results promising. Droperidol has been combined with pure agonistic as well as partial antagonistic opioids (buprenorphine), and in both cases with success.

Extradural neuroleptics may be beneficial when patients suffer from pain which is not eliminated by means of extradural opioids alone.

V. BACH
P. CARL
O. RAVLO
M. CRAWFORD
L. KRUSE
Esbjerg, Denmark

REFERENCES

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AN UNUSUAL CASE OF SINUS ARREST

Sir,—We read with much interest the brief communication "An unusual case of sinus arrest", reported by Kirkwood and Duckworth (1983). The authors pointed out that vecuronium could, possibly, have caused sinus arrest. We would like to stress some details, for their consideration:

(1) Lack of atropine in premedication.

(2) Repeated administration of opiates, during induction of general anaesthesia and later for maintenance of analgesia. Opiates do cause bradycardia.

(3) Sinus arrest occurred 17 min after first administration of vecuronium.

(4) After administration of atropine, two further doses of vecuronium did not produce disturbance of rhythm.

After having considered the above points, do the authors really think that vecuronium had any responsibility in the sinus arrest they reported?

E. Maestrone
G. Pradella
Sondrio

REFERENCE

Kirkwood, I., and Duckworth, R. A. (1983). An unusual case of sinus arrest. *Br. J. Anaesth.*, 55, 1273.

Sir,—Thank you for giving me the opportunity to reply to the points raised by Drs Maestrone and Pradella.

It was not intended to suggest vecuronium was responsible *per se* for the sinus arrest. The case was reported to emphasize that anaesthesia using agents known to cause bradycardia, such as opiates and halothane, in conjunction with so-called "clean" myoneural blockers such as vecuronium and atracurium, may result in bradycardia which may be severe, or even, as in this patient, sinus arrest.

In common with many anaesthetists in the U.K., it has not been my practice to prescribe atropine routinely as part of premedication for some time. Atropine is, however, kept at hand so that small but suitable doses may be given i.v. to obtain the correct degree of block of the cardiac vagus, indicated by continuous ECG monitoring. This assumes particular importance when a neuromuscular blocking drug devoid of cardiac side-effects, such as vecuronium, is used, and bradycardia caused by other drugs is uninhibited and may be severe.

The report of this case was intended to draw attention to these points.

I Kirkwood
Glasgow

DIFFICULT INTUBATION

Sir,—A gum-elastic bougie can be a valuable aid to the intubation of the trachea when the larynx is difficult to see, and when anatomical factors prevent the tube from being directed into the trachea. However, after successful passage of a bougie it may be difficult or impossible to slide the tube around it (Boys, 1983). When the tube is simply pushed down around the bougie lying in the trachea (fig. 1A) the tip of the tube is liable to lodge on the right vocal cord. Encountering resistance, one automatically tends to rotate it clockwise, as if inserting a bolt or screw, thus causing the tip of the tube to lie posterior to the bougie, protruding like a ploughshare (fig. 1B) lodging firmly behind the arytenoids. I suggest that, before the tube nears the larynx, it should be rotated a quarter-turn anti-clockwise. This manoeuvre will cause the tip of the tube to lie anterior to the bougie, and to be in close contact with the bougie, so that it does not catch on anything (fig. 1C). The tube must previously have been lubricated inside and outside.

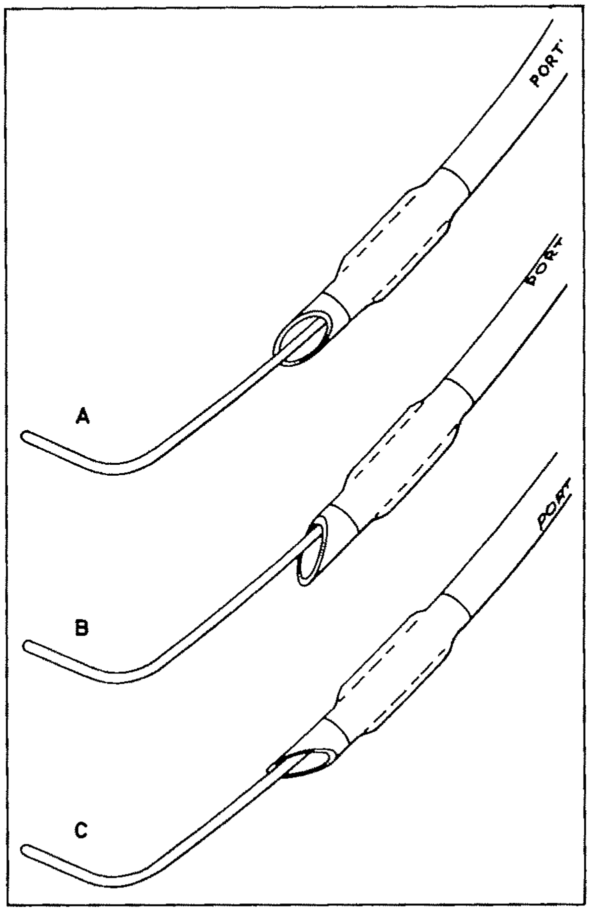

FIG. 1. A: Tip of tube in a position liable to lodge on right vocal cord. B Clockwise rotation of tube may lead to the tip becoming lodged behind the arytenoids. C One-quarter turn anti-clockwise of the tube brings it in close contact with the bougie, preventing lodgement.

I have tested this technique in more than 100 patients, some of whom would otherwise have been difficult to manage, and have found it has always been successful and atraumatic.

The quarter-turn anti-clockwise twist of the tube on the bougie is applicable also to nasal intubation. Perhaps it would be helpful in "guided blind intubation" when the tube tends to slip into the oesophagus (Akinyemi and John, 1974).

P. S. Cossham
Leicester

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Akinyemi, O. O., and John, A. (1974). Case report: A complication of guided blind intubation. *Anaesthesia*, 29, 733.
Boys, J. E. (1983). Failed intubation in obstetric anaesthesia, a case report. *Br. J. Anaesth.*, 55, 187.

BLIND NASOTRACHEAL INTUBATION GUIDED BY AN IMAGE INTENSIFIER

Sir,—According to Alexopoulus, Larson and Lindholm (1983), the airway aerogram obtained with x-rays is easily identifiable along its anterior aspect, from the epiglottis to about 60 mm below the vocal chords.

Based on this evidence, and to avoid problems arising from technical difficulties during blind nasotracheal intubation, we have successfully used an x-ray image intensifier to guide the introduction of the tracheal tube between the vocal chords.

We place the patient in a supine position, the head resting on a pillow 8–10 cm above the plane of the operation table. After good topical anaesthesia, the image intensifier is positioned so as to obtain a lateral x-ray view of the oropharyngotracheal aerogram. In this manner it is easy to identify basic anatomical structures such as hyoid bone, epiglottis, Morgagni's ventricles and the trachea. Once these elements are recognized on the screen, the endotracheal tube is inserted in the correct position.

We consider that this technique can be useful during difficult blind nasal intubation.

F. GONCALVES
P. ANDRADE
Caracas, Venezuela

REFERENCE

Alexopoulos, C., Larson, S. G., and Lindholm, C. E. (1983) Anatomical shape of the airway. *Acta Anaesthesiol. Scand.*, 27, 189.

0.75% BUPIVACAINE

Sir,—I write in full support of the Editorial views expressed by Dr Scott in your May (1984) issue, and also to comment on the paper from Thorburn and Moir in the same issue.

In this hospital we used 0.75% bupivacaine for Caesarean section for approximately 1 year following general availability of the solution in this country. After that time we abandoned its use because we were not satisfied that it provided a sufficiently superior standard of analgesia to compensate for some apparently related drawbacks, as detailed below. However, reception of the curt notice, from the distributors of the drug, to the effect that 0.75% bupivacaine was stigmatized as being contraindicated for use in obstetric practice was greeted with incredulity and (in common with Dr Scott and many others) resentment. There had been no consultation with those members of our specialty who are acttively involved in this field. Furthermore, there has, as far as I am aware, been no instance of cardiac arrest—fatal or non-fatal—relating to the use of 0.75% bupivacaine in U.K. obstetric practice. There have been convulsions resulting, but they have been successfully treated in the orthodox manner. Perhaps, the female in the U.S.A. responds to high-dose bupivacaine differently from her British counterpart (and that is a possibility—remember the contrasting response to skeletal muscle relaxants).

Detailed in table I are data respecting the dose of bupivacaine (invariably the plain solution has been used) administered in our most recent series of 606 cases of elective Caesarean section (with the exceptions of those in which some top-ups consisted of 0.75% and others of 0.5% bupivacaine, and a few in which full details of dosage are missing).

TABLE I. *Dose of bupivacaine (mean and range) administered to mothers undergoing elective Caesarean section, categorized in respect to the time elapsing between injection of the first and last top-up dose before the start of operation, and the concentration of drug solution used*

	Interval first–final pre-delivery dose (min)	*n*	Bupivacaine dose (mg) Mean	Range
0.5% Solution				
	<45	195	143.7	60–335
	45–75	159	177.3	90–335
	>75	85	169.1	60–355
0.75% Solution				
	<45	97	201.8	105–300
	45–75	38	263.7	165–532.5
	>75	32	303.7	142.5–525

Of the 439 mothers who received 0.5% bupivacaine, one was rendered drowsy (150 mg in 70 min) and another disorientated (115 mg in 33 min). Of the 167 mothers who received 0.75% bupivacaine, one developed slurred speech (525 mg in 76 min) and another became drowsy (225 mg in 48 min). One further mother, not included in the table, convulsed after an injection, through the extradural cannula, of 75 mg (0.75% solution). That was undoubtedly an i.v. injection—the mother recovered rapidly and neither she nor her infant came to harm.

Additionally, eight (4.8%) of the mothers given 0.75% bupivacaine required ephedrine to correct hypotension—an unacceptably high incidence. Three mothers (0.7%) given 0.5% bupivacaine received ephedrine.

In view of the higher incidence of CNS complications and hypotension, we abandoned the use of the stronger solution. However, our experience with the 0.5% solution suggests that Thorburn and Moir are rather over-cautious in their advocacy. I have not related the dose received by each mother to her weight, but it is infrequently that we temper the volume of solution injected to the stature of the patient. In only a small minority of our patients does their weight at term lie outside the range 70–90 kg.

Assuming a mean weight of 80 kg, the average dose—using the 0.5% solution—administered during the period 45–75 min, was 22 mg kg^{-1} h^{-1}. Although I do not wish to suggest that anaesthetists can be profligate in their use of bupivacaine, I do content that, in British practice at least, its bounds of safety are considerably greater than those intimated by the manufacturers.

J. SELWYN CRAWFORD
Birmingham

Sir,—We are grateful for the opportunity to comment on Dr Selwyn Crawford's letter. Most of his letter concerns the editorial by Dr Scott, and the manner in which the recommendation of use of 0.75% bupivacaine in obstetric anaesthesia was withdrawn, and we do not propose to comment on this aspect.

Like Moore and his colleagues (1977), Dr Crawford believes that the manufacturer's recommended maximum dose of bupivacaine is too restrictive, and to practise within those limits is over cautious. We too have exceeded the recommended dose, but the purpose of our case reports was to draw attention to the fact that we had observed convulsions in two patients who received a total dose of 0.5% bupivacaine, following extradural analgesia in labour using 0.375% bupivacaine, which exceeded the manufacturer's recommended maximum of 2 mg $kg^{-1}/4$ h. One disturbing aspect of the cases reported was the total absence of premonitory warning signs or symptoms; neither drowsiness or slurring of speech was a feature. This suggests that perhaps the only guide to the possible onset of toxic reactions is the total dose injected.

It is quite clear that the manufacturer's maximum dose has been exceeded by a considerable margin in some patients, but it is the boundary, below which it is safe for all patients, that is difficult to define. We no longer feel that the manufacturer's recommendation can be exceeded with impunity, and that the risk is greater when the patient has already received continuous extradural analgesia in labour. This risk may be reduced by using concentrations of 0.25% bupivacaine or less during extradural analgesia in labour.

The use of a low concentration in labour and a high concentration for subsequent Caesarean section will minimize the total exposure to bupivacaine.

J. THORBURN
D. D. MOIR
Glasgow

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Moore, D. C., Mather, L. E., Bridenbough, L. D., Thompson, G. E., Balfour, R. I., Lysons, D F., and Horton, W. G. (1977). Bupivacaine (Marcaine): an evaluation of its tissue and systemic toxicity in humans. *Acta Anaesthesiol. Scand.*, **21**, 109.

Sir,—I was concerned to read the report of two patients who had grand mal convulsions after receiving large amounts of extradural bupivacaine for Caesarean section (Thorburn and Moir, 1984). Whilst a strong advocate of the extradural technique originally described by Thorburn and Moir (1980), whereby part of the total dose of local anaesthetic is given with the patient sitting and a further dose (or doses) given with the patient lying down, I feel that some other method rather than simply adding more and more local analgesic should be used in the case of "recalcitrant" extradurals which are difficult to extend high enough for Caesarean section, although others similarly (Crawford, 1980) have advocated very large doses of bupivacaine.

A likely anatomical explanation for the difficulty in extending some extradural blocks has been elegantly shown by Husemeyer and White (1980), whose polyester resin studies in cadavers showed in some cases a remarkable tendency to "compartmentalization" in the extradural space. If the extradural catheter is inadvertently placed in one of these "compartments", spread of local analgesic solution can only occur to other parts of the extradural space with a degree of difficulty which depends on the ease of escape of the solution from the "compartment". This may be the explanation why, in some patients, very large volumes of solution may eventually be successful in achieving the required extent of spread.

A more rational approach to the problem of these "difficult" extradurals would seem to be to move the catheter tip to a site where it may be more effective. This can sometimes be achieved by withdrawing the catheter slightly and this writer would often do this before injecting a relatively modest third or fourth dose of local analgesic with the patient head-down (difficulty in cephalic spread being the usual problem). If these measures do not produce the required extension of the block, one of two more reliable (and safer from a toxicity viewpoint) techniques are used.

(1) A thoracic extradural may be carried out at a level physically above the apparent block to the spread of analgesic solution, for example if there is difficulty in extending the block above T11, an extradural would be performed at the T8–9 or T9–10 level. For those anaesthetists who habitually use the paramedian approach to the lumbar extradural space, the change from the lumbar to the thoracic region presents only a minor change in technique (Carrie, 1977). As the local anaesthetic is then deposited in the centre of the area where analgesia is required, a relatively small increment of solution, for example 5–6 ml of 0.5% plain bupivacaine invariably completes the analgesia.

(2) Subarachnoid block may be added. While this writer would probably use a 26-gauge spinal needle through the extradural needle using 0.5% plain bupivacaine (Carrie and O'Sullivan, 1984), those less familiar with this method could use a more conventional hyperbaric spinal technique. The dose of local anaesthetic required is so small that it adds almost nothing to the risk of toxicity. This technique would be preferred to the thoracic method in patients in whom the extent of blockade obtained by the lumbar extradural was so limited as to make it seem unlikely that the required extent of analgesia could be completed with a small dose of local anaesthetic in the thoracic extradural space.

Most obstetric patients, having made the decision to have their Caesarean section awake, are most disappointed if failure to achieve adequate blockade necessitates general anaesthesia, and they are only too willing to accede to one of the above additional regional techniques. Given a patient who is willing to persevere (as she usually is), an anaesthetist who is willing and able (as he or she should be) and a surgeon who will wait (as he must, if general anaesthesia is to be avoided), it should be possible to provide regional analgesia for any Caesarean section without running the risk of local anaesthetic overdose. Whilst there may be argument as to what is a safe dose of bupivacaine and to what amount this can be increased as the period of time over which it is given is extended, if the manufacturer's recommendation of a maximum dose of 2 mg kg^{-1} in a 65-70 kg adult given over a 4-h period is to be taken as a reasonable guide, with the above techniques it should seldom need to be exceeded.

Drs Thorburn and Moir are to be thanked for their frankness in reporting these cases, and it is to be hoped that their communication will prevent others from falling into the same local analgesic "toxicity trap".

L. E. S. CARRIE
Oxford

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MEDICAL GAS DELIVERY SYSTEMS

Sir,—I would like to comment on the article by Hosken, van Hasselt and Moyes (1983) on Medical Gas Delivery Systems. The idea of differential pressures has much to commend it as a safety feature, especially with high pressure mixer valves (Thorp and Railton, 1982).

In describing the use of pneumatic valves, no mention is made of the on–off characteristics of the Festo UV adjustable pressure actuator. Many similar devices have a switching pressure which depends upon whether the pipeline pressure is increasing or decreasing. With a decreasing pipeline pressure the alarm may actuate at a pressure lower than 480 kPa.

Valves 4, 6 and 7 appear to have no adjustable pressure actuator connected to them. Presumably the actuating gas line is connected directly to a diaphragm within the valve. This implies that two different gases would be separated only by this diaphragm. Therefore, it would seem possible for nitrous oxide to enter the downstream air line if the medical air supply failed and there is a defect in the diaphragm or seal of valve 6.

An alternative approach would be to use valves actuated mechanically by a push-rod which is moved by a miniature pressure actuator. This would completely separate the two gases.

It may be preferable to control the nitrous oxide line directly from the oxygen line, allowing the system to be used without air and providing closer control over the most hazardous situation, that of 100% nitrous oxide.

Lastly may I make a plea for fewer whistles. Five may be too many for some anaesthetists and could lead to confusion.

R. W. Boaden
Bristol

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Hosken, K. A., van Hasselt, C. H., and Moyes, D. G. (1983). A system of differential delivery pressure and hose diameters for use in hospital medical gas installations. *Br. J Anaesth.,* 55, 891.

Thorp, J. M., and Railton, R. (1982). Hypoxia due to air in the oxygen pipeline. *Anaesthesia,* 37, 683.

Sir,—Dr Boaden has correctly made reference to the fact that there is a pressure differential between the activating pressure of the Festo UV on increasing pressure and the lower de-activating pressure on decreasing pressure. This feature is incorporated into the design of the Kentel Unit (Hosken, van Hasselt and Moyes, 1983). The oxygen pressure sensitive valve will activate when the pressure reaches or exceeds 480 kPa, but once activated, will allow the oxygen pressure to decrease to 420 kPa before deactivating. This provides for small pressure decreases which occur as a result of sudden or large variations in the demand for oxygen in nearby theatres without causing unnecessary false alarms on the Kentel unit.

Valves 4 and 7 are activated by oxygen already verified by valve 1, and valve 6 by medical air verified by valves 2 and 3. Therefore the activators of valves 4, 6 and 7 need not be adjustable. The valves 4, 6 and 7 are indeed of a type which, to quote Dr Boaden, are "activated mechanically by a push-rod which is moved by a miniature pressure activator". These valves were carefully selected as a type which would ensure complete separation of gases, even under fault conditions.

The nitrous oxide can optionally be directly controlled by oxygen or, as illustrated, indirectly by oxygen since the air line is first controlled by oxygen. This provides a second line of defence as both oxygen and medical air must be correctly available before nitrous oxide can be used.

We appreciate the desire for fewer whistles and, in fact, all of the alarm circuits can be routed to a single whistle, provided that each line has a positively effective non-return valve to prevent cross-feeding of gases. In this case we opted for a duplication of whistles as they are considerably cheaper and perhaps more effective as an alarm.

K. A. Hosken
Johannesburg

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Hosken, K. A., van Hasselt, C. H., and Moyes, D. G. (1983). A system of differential delivery pressures and hose diameters for use in hospital medical gas installations. *Br. J. Anaesth.,* 55, 891.

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BOOK REVIEWS

Anaesthesia Review 2. Edited by L. Kaufman. Published by Churchill Livingstone. Pp.228; indexed; illustrated. Price £12.00.

Dr Kaufman has selected the subject matter extremely carefully, to produce a book which appears to touch on most things of importance to anaesthetists. The mechanisms of both general anaesthesia and local anaesthesia are discussed. Pain is considered in depth, in respect of the physiological aspects of pain perception and of narcotic analgesia, including extradural and intrathecal narcotics. There are chapters on paediatric anaesthesia, closed circuit anaesthesia and non-invasive monitoring. Even regurgitation and aspiration find a place. The book commences well, with relevant recent advances in medicine and the sleep apnoea syndrome.

It is a pity that the inclusion of references in the text has not followed the form adopted by the U.S. National Library of Medicine and used in *Index Medicus*. For a review to be valuable, it must be well referenced and these reviews are no exception in this respect. However, the inclusion of the authors' names in the text does make easy reading more difficult and interrupts a train of thought. Nonetheless, I found the chapters and their content to be extremely interesting and likely to be effective in keeping the reader up to date in those aspects of the discipline with which he may be less familiar as a result of limited contact. Some comments in the book are, of course, more up-to-date than others. One would expect and, indeed, finds that the references in the Appendix are more up to date than some of those in the main body of the book itself. Indeed, most quote papers published in the 1980's. This cannot be said about each of the other chapters, and in some respects I feel that a Review, presumably aimed at updating the reader, should not contain so many references already available to the reading public when the previous edition appeared. The value of these kind of Reviews is that they alert the anaesthetist to situations and conditions which, although they may be extremely rare, may prove very hazardous to patients. The sleep apnoea syndromes mentioned in the first chapter and detailed in the second chapter could be such a condition. Of particular interest was the review of pulmonary complications following general anaesthesia. Dr Jones has restated the factors which predisposed to pulmonary complications and he has considered management and response. While he reminds us that adequate pain relief and physiotherapy have not been shown to ameliorate the respiratory effects of surgery, he admits that few would be prepared to look after patients in the intensive care unit without the aid of a physiotherapist. The mechanisms of action of antibiotics are discussed in detail, but this is a chapter that requires re-reading a number of times lest ignorance is replaced only by confusion. The allergic responses chapter is wide-ranging, although it might confuse the clinical anaesthetist. The value of skin tests is discussed very clearly. This is a complex subject, and the response to some drugs such as neuromuscular blockers is indeed controversial. For those interested in the direction in which anaesthesia may move in the future, the last paragraph of Chapter 10 is pertinent. "A new and powerful idea has emerged that the pharmacology of the spinal cord is accessible to anaesthetic practice. Eventually this may be the principle of the principles".

In conclusion, this is an excellent book. In some parts it is a little hard going and in others it is straightforward, but every anaesthetist would benefit from reading it at least once. Some of our accepted practices are questioned, and that is the way progress is made.

T. E. J. Healy

An Integrated Approach to Monitoring. Edited by J. S. Gravenstein, R. S. Newbower, A. K. Ream and N. Ty Smith. Published by Butterworths. Pp.243; indexed; illustrated. Price £32.00.

Perhaps part of the art of medicine is to assess the state of health of a patient from the value of, rate of change of and association between the various variables that developments in science now allow the clinician to measure. Often, the physiological quantities actually monitored are chosen simply because equipment or transducers are available to make the measurements. Sometimes, only an assessment of the average performance of an organ such as the lung can be made, and it may be impossible or impracticable to monitor the variable which is really of interest. The problems of determining the state of the patient and his prognosis by the use of multiple and imperfect measurements are examined in this book. While multiple measurements are becoming easier and perhaps more routine, there is the increasing problem of interpreting all the information presented. Naturally, computers play a large part in overcoming this problem and the latter part of the book concentrates on developments in computer programming and the interaction between the computer and the user. Currently, the principal concerns in the use of computers are data security and confidentiality, but the introduction of systems which aid the decision-making process of the clinician rather than simply record information raise further legal issues. For example, what are the consequences of using, not using or ignoring the advice of computer-aided decision-making systems?

This book considers such matters in the form of various selected topics extracted from quite a wide field of interest. The book comprises 17 chapters in four sections: monitoring the cardiovascular system, monitoring the respiratory system, the use of modelling and the problems associated with the handling of large amounts of information. Chapter 16 is an analysis of computer-aided decision making in nuclear plants and strays a little from the otherwise direct consideration of medical topics. As each chapter has different authorship, there is a noticeable lack of continuity in the book, which reads more like a conference report than a progressive treatment. However, the editors have not sought to be comprehensive, but to present selected examples of some of the thinking in the field of physiological monitoring. There are useful references at the end of each chapter and these are needed, because the topics are treated in a rather concise manner. A good grasp of mathematics is necessary to understand fully the arguments in some of the chapters. This book is nevertheless interesting and well worth reading, because the matters examined probably form the basis of future research and development in patient monitoring.

P. D. Davis

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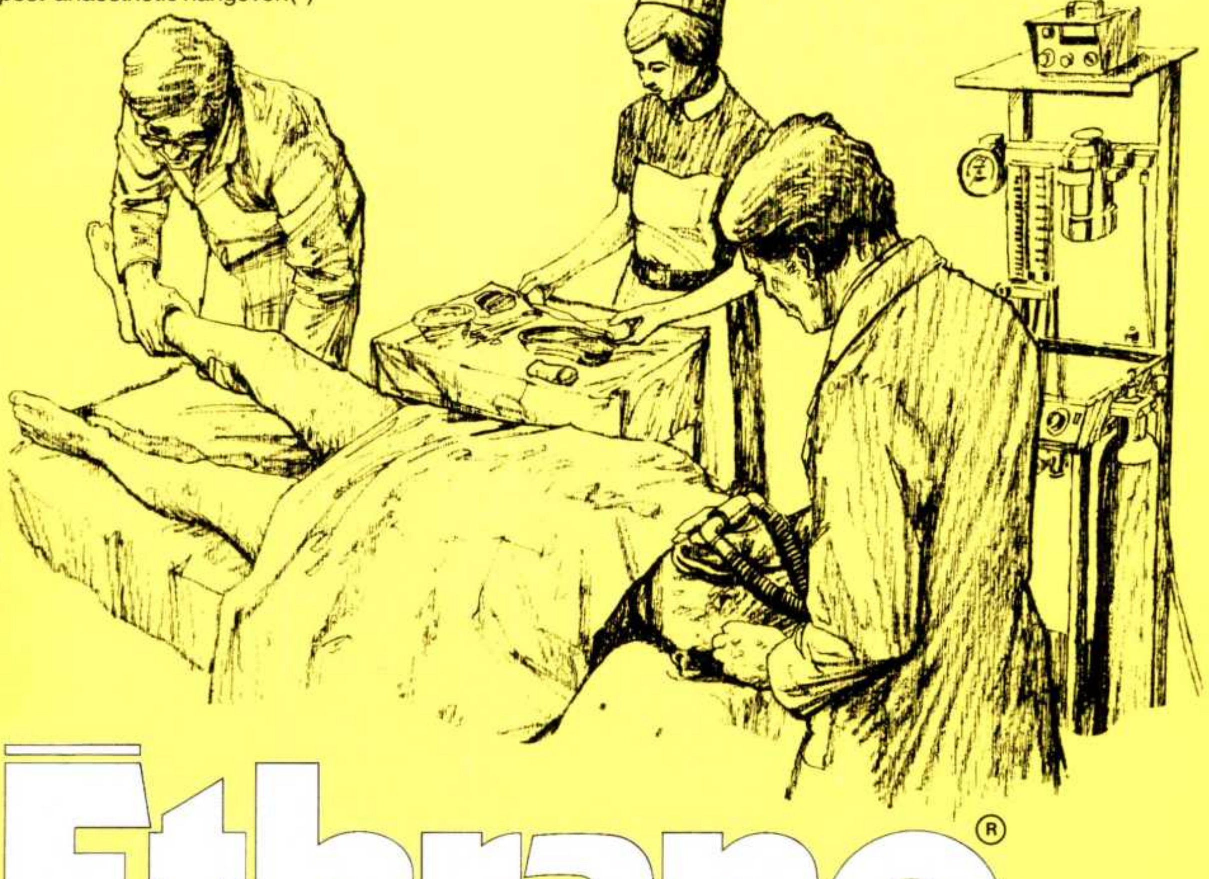

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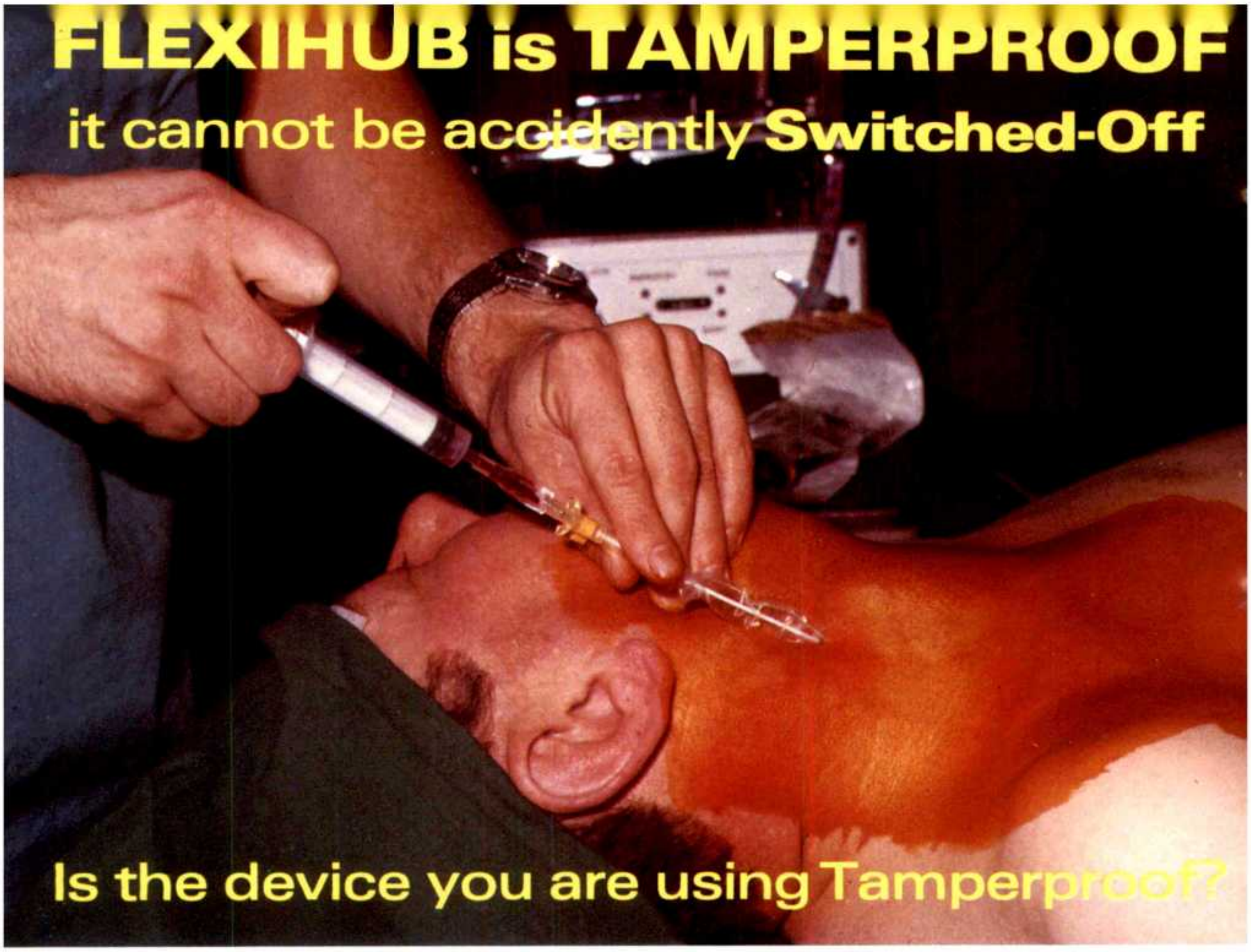
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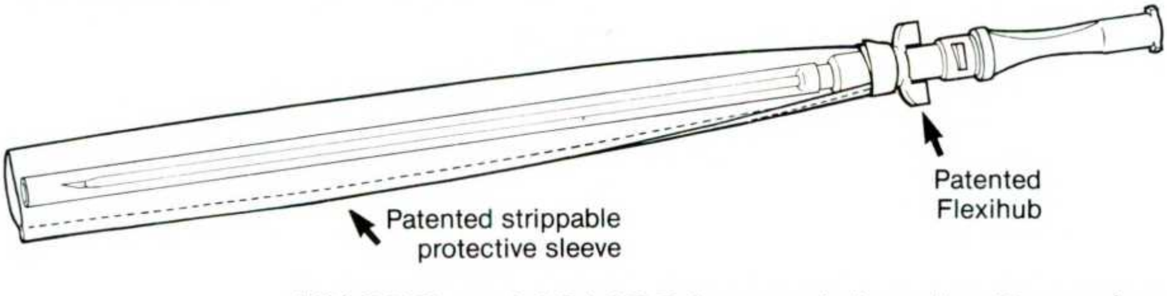

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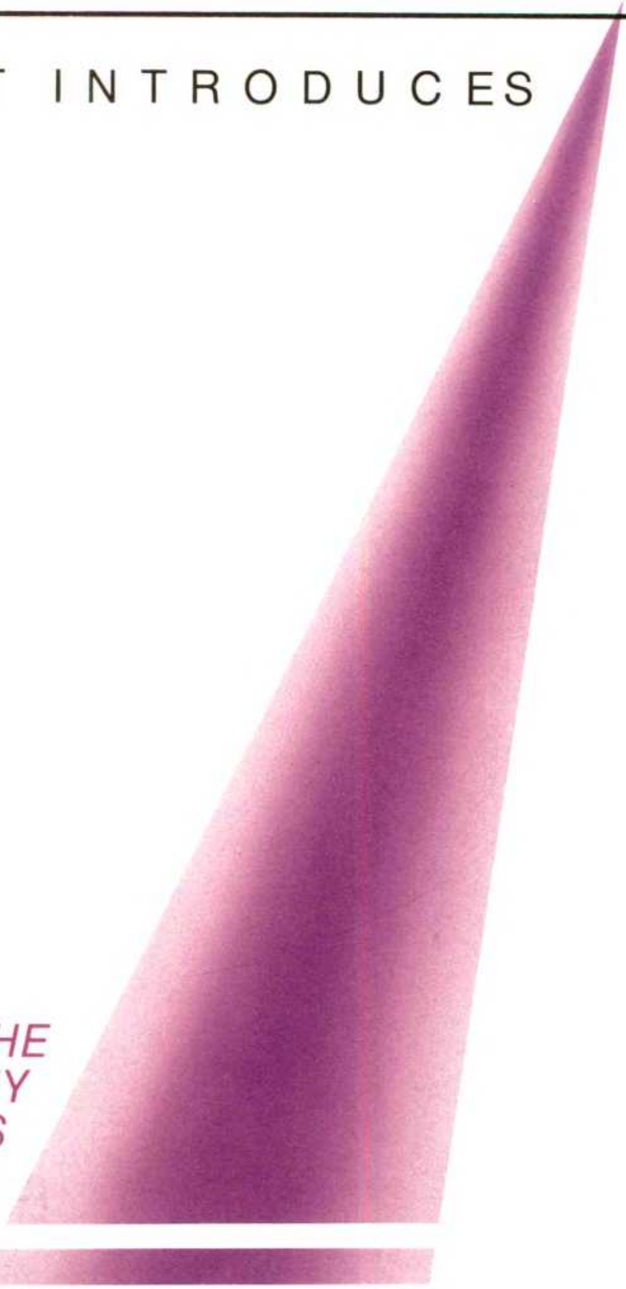

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There is minor depression of cardiac output during anaesthesia with Forane. A decrease in systemic vascular resistance reduces afterload, thus stroke volume is well maintained. Forane has also been shown to have minimal dysrhythmogenicity even in the presence of catecholamines.[5,6]

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Muscle relaxants are markedly potentiated with Forane, the effect being most profound with the non-depolarizing type. The result – reduced dosages, few side effects.

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References

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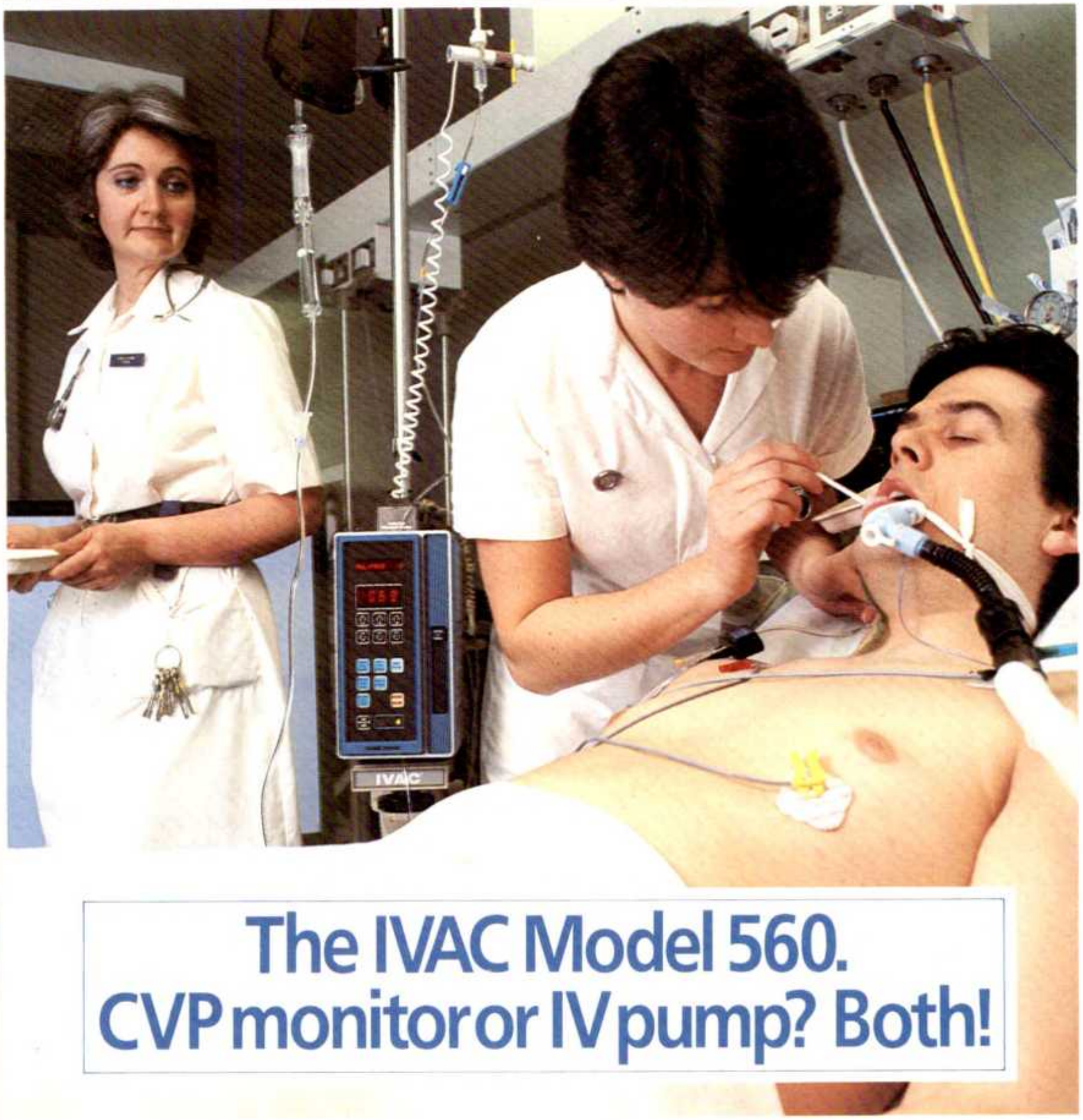

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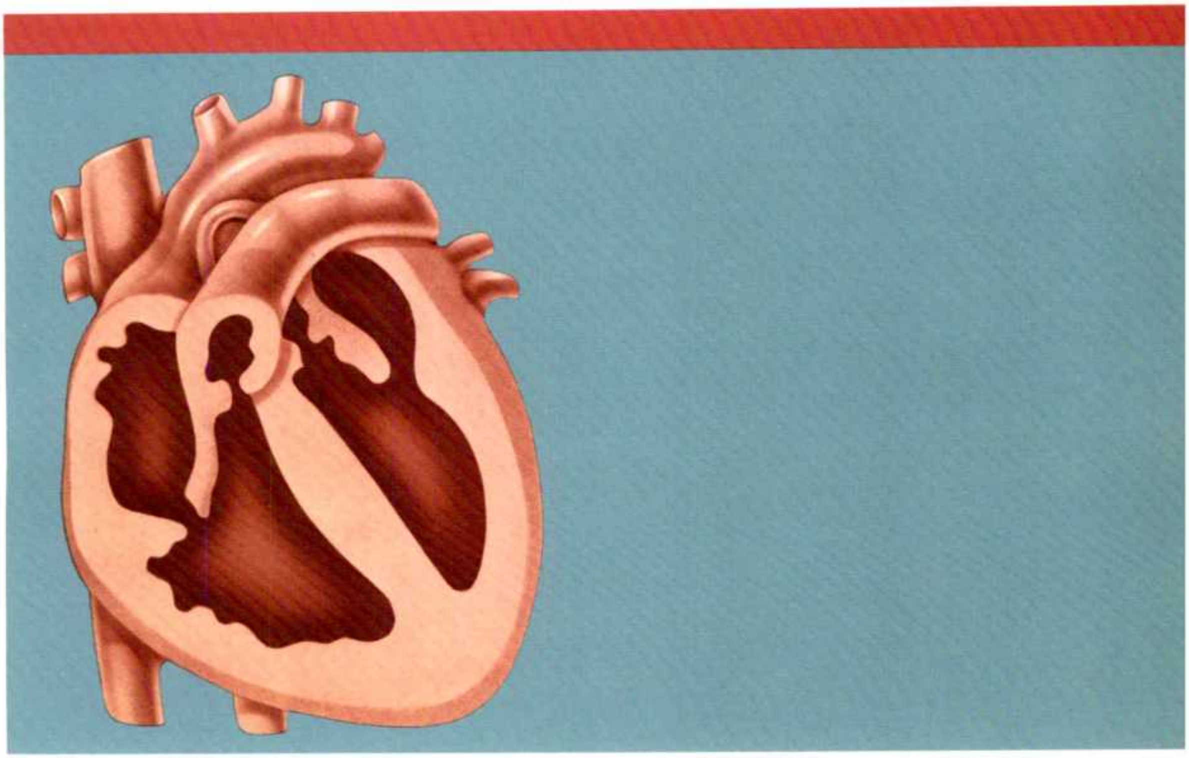

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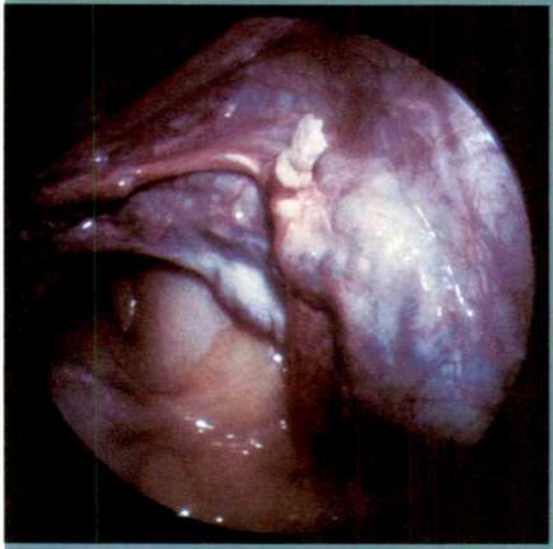

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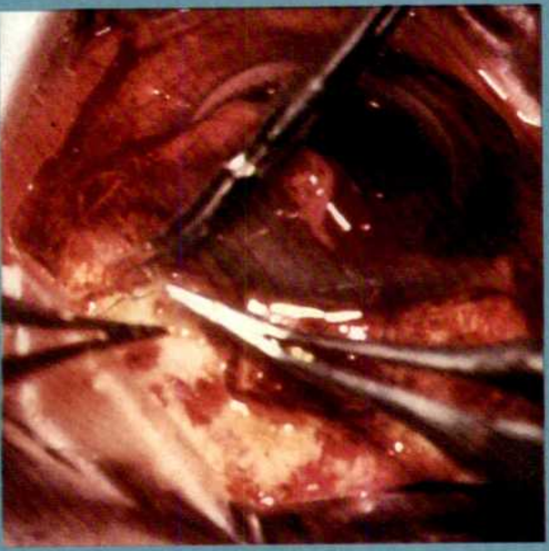

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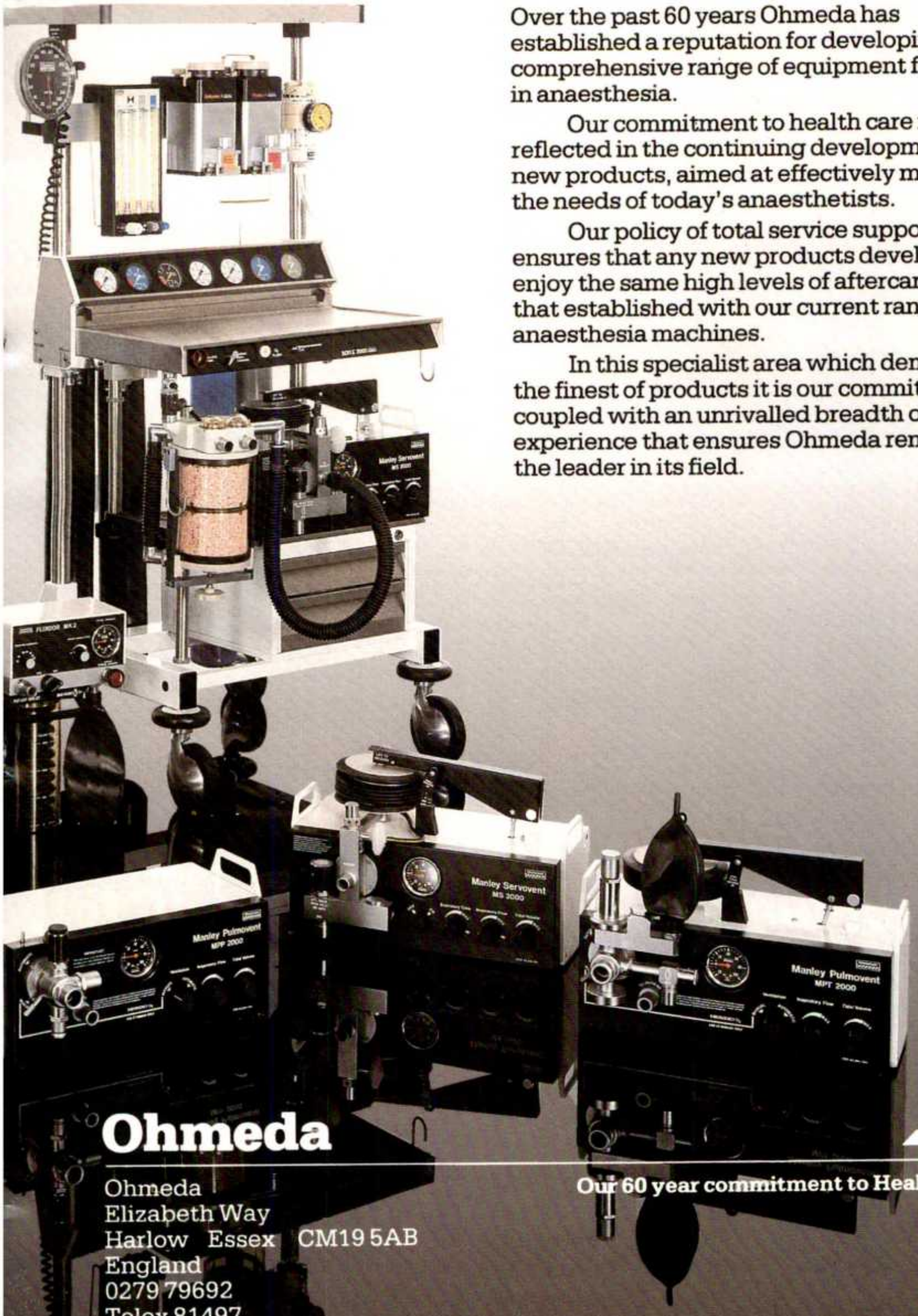

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Faculty of Medicine, University of Leiden, the Netherlands

International Course on
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May 9–10, 1985
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- Interpretation of recent cardiac evaluation techniques
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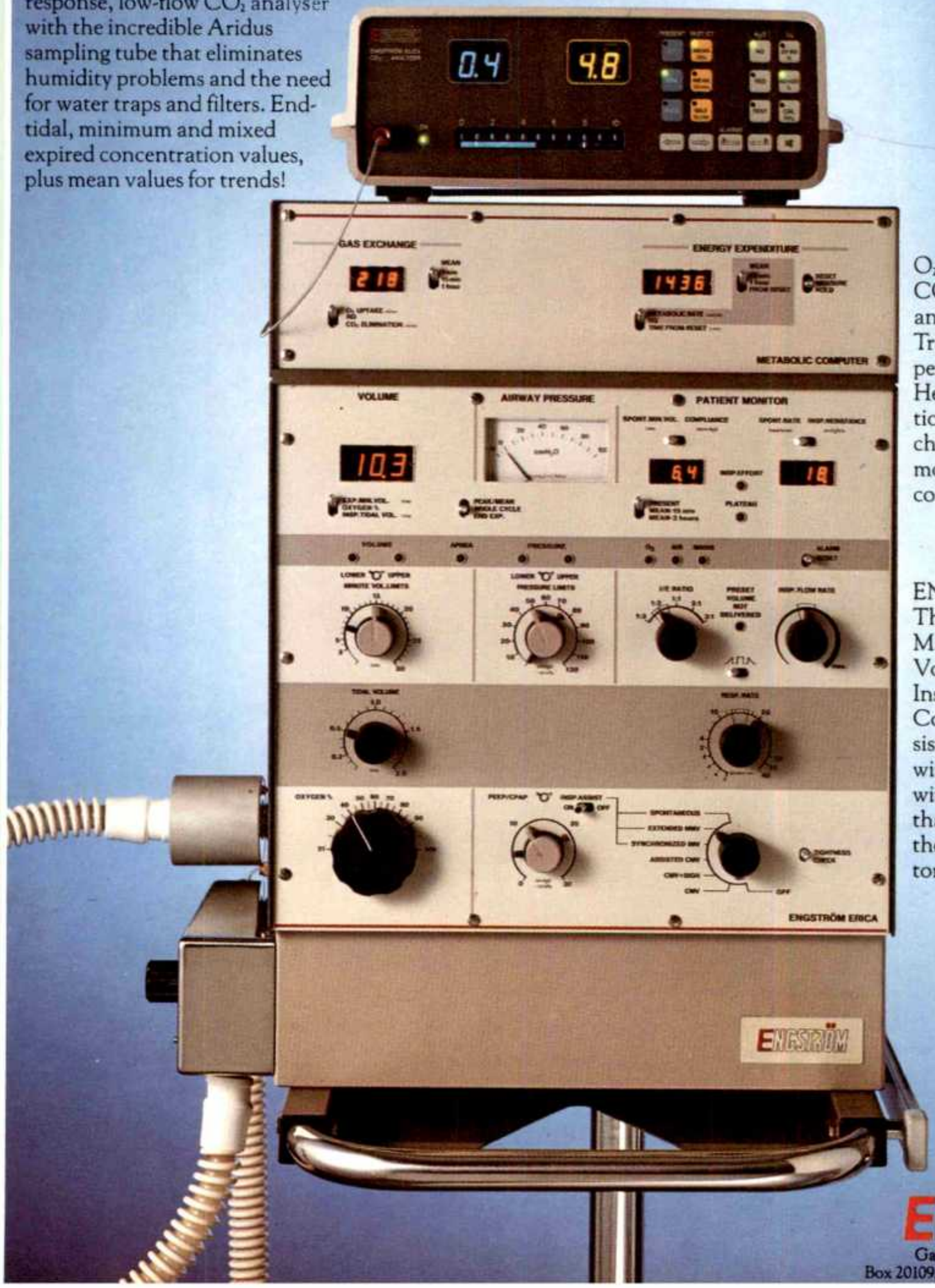

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EDITORIAL

DEADSPACE, INVASIVE AND NON-INVASIVE

Recent years have seen the advent of several compact and reliable devices which can monitor the expired carbon dioxide concentration or volume, or both. The Siemens–Elema Analyzer 930 is intended for use with the Servo Ventilator, from which it obtains flow and timing signals. This enables it to calculate the volume of expired CO_2 and, together with suitable recording devices, present the CO_2 single breath test (see below). Other devices (Datex Normocap, Hewlet–Packard 14360A, Siemens–Elema Monitor 130, Eliza Duo) which lack a flow signal input, measure only CO_2 concentration, but can be used in a variety of situations. In particular, they measure the end-tidal $P\mathrm{CO}_2$ or CO_2 fraction ($P\mathrm{E}'_{CO_2}$ or $F\mathrm{E}'_{CO_2}$). Both types of device give valuable information about gas exchange during anaesthesia and mechanical ventilation, or both. The object of this review is to analyse this information and describe how it can be used with and without the knowledge of arterial $P\mathrm{CO}_2$ (Pa_{CO_2}).

Throughout this review I will use as a basic tool the single breath test for CO_2, SBT-CO_2 (Comroe, 1962; Fletcher, 1980). This relates the expired CO_2 fraction ($F\mathrm{E}_{CO_2}$) to expired volume (fig. 1). The tracing is divided into three phases: phase I, comprising CO_2-free gas from the airways; phase II, a transition phase; and phase III, comprising CO_2-bearing gas from the alveoli. Phase III almost always has a positive slope, that is the last gas to reach the airway opening has the greatest $F\mathrm{CO}_2$.

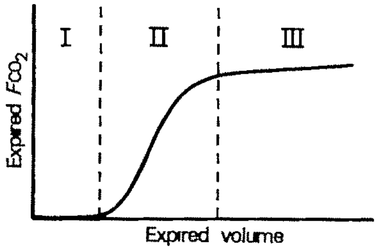

FIG. 1. The three phases of SBT-CO_2. Phase I is the CO_2-free part of the breath, phase II is a transition phase and phase III is the CO_2-bearing part.

Bohr's deadspace

The concept of respiratory deadspace was first described by Christian Bohr (1891) in a German language paper. He used the term schädliche Raume (damaging space) to describe that part ($V\mathrm{D}$) of the tidal volume ($V\mathrm{T}$) which did not take part in gas exchange. Using SBT-CO_2 we can illustrate Bohr's concept (fig. 2). The volume of CO_2 in the breath ($V\mathrm{T}_{CO_2}$) is the product of the gas volume reaching the alveoli ($V\mathrm{A}$), and its concentration ($F\mathrm{A}_{CO_2}$). ($F\mathrm{A}_{CO_2}$ was sampled at the tracheal bifurcation at the end of expiration.) $V\mathrm{T}_{CO_2}$ is equal to area X in figure 2. Thus:

$$V\mathrm{A} = V\mathrm{T}_{CO_2}/F\mathrm{A}_{CO_2}$$

$V\mathrm{T}_{CO_2}$ was obtained from

$$V\mathrm{T}_{CO_2} = V\mathrm{T} \times F\mathrm{E}_{CO_2}$$

where $F\mathrm{E}_{CO_2}$ was the mixed expired fraction of CO_2 collected in a bag.

Since $V\mathrm{T} = V\mathrm{D} + V\mathrm{A}$, rearrangement yields:

$$V\mathrm{D}/V\mathrm{T} = 1 - F\mathrm{E}_{CO_2}/F\mathrm{A}_{CO_2} \qquad (1)$$

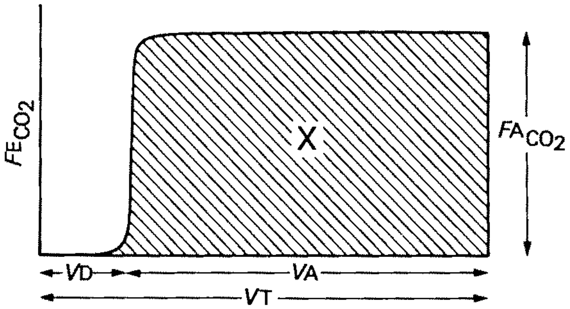

FIG 2. A diagrammatic representation of Bohr's original deadspace concept. The area under the tracing, X, is the volume of CO_2 in the breath.

Because Bohr probably imagined the alveolar gas to be homogenous, the $V\mathrm{D}$ so obtained was believed to represent the volume of the airway down to the point where gas exchange commenced.

In the early part of this century, similar measurements were performed on human volunteers in Oxford (Haldane and Priestly, 1905), and Copenhagen (Krogh and Lindhard, 1917), sampling end-tidal gas at the mouth. The Danes took the end-tidal $F\mathrm{CO_2}$ ($F\mathrm{E'_{CO_2}}$) of tidal breaths as a measure of $F\mathrm{A_{CO_2}}$, and this gave them values for $V\mathrm{D}$ of about 150 ml, which agreed well with cadaver measurements. The Englishmen obtained greater values for $F\mathrm{E'_{CO_2}}$ by sampling from forced expirations. Increase $F\mathrm{E'_{CO_2}}$ increases the term $(1 - F\mathrm{E_{CO_2}}/F\mathrm{E'_{CO_2}})$, accounting for the values of 600 ml which they obtained for $V\mathrm{D}$.

How did this come about? The effect of a forced expiration was to increase $V\mathrm{T}$ and, thus, increase $F\mathrm{E'_{CO_2}}$, since phase III has a slope. One reason for this is the stratified inhomogeneity which exists within the lung, so that the greater the tidal volume, the less $F\mathrm{E'_{CO_2}}$ is typical of mean alveolar $\mathrm{CO_2}$.

Over the years, the comparison of the $F\mathrm{CO_2}$ of end-tidal and mixed expired gas has become known as Bohr's method. It is described in Nunn (1977) as an undergraduate experiment for measuring the volume of the airways and, thus, the students perform a repeat of Bohr's work. In order to distinguish this "non-invasive" deadspace from the deadspace obtained with arterial blood sampling, I suggest the $V\mathrm{D}$ measured from $F\mathrm{E'_{CO_2}}$ be referred to as $V\mathrm{D^{Bohr}}$

Airway deadspace

The volume of the fresh gas volume down to the alveolar/fresh gas interface may be regarded as the (convective) airway deadspace ($V\mathrm{D^{aw}}$) (Fletcher et al., 1981). I prefer the term $V\mathrm{D^{aw}}$ to the older term—anatomical deadspace—because $V\mathrm{D^{aw}}$ can be changed by many factors, such as breathholding and inspiratory gas flow pattern and has, thus, little to do with anatomy. Because of the conceptual difficulties of measuring this volume from end-tidal gas, several graphical methods for determining $V\mathrm{D^{aw}}$ have been developed. Of these, the best known is the "equal area method" (Aitken and Clarke-Kennedy, 1928; Fowler, 1948). Other methods (Langley et al., 1975; Cumming, 1980) give similar results and are more suitable for computer treatment.

Graphical methods for $V\mathrm{D^{aw}}$ are difficult to apply to "bedside" monitoring. However, phase I volume, the expired volume at which $\mathrm{CO_2}$ first appears, is easier to measure: the $\mathrm{CO_2}$ Analyzer 930 describes it as "ineffective tidal volume". In 87 intubated adult patients investigated during anaesthesia with IPPV, I found the following relationship at tidal volumes of about 500 ml:

$$V\mathrm{D^{aw}}\ (\mathrm{ml,\ ATPS}) = 1.30 \times \text{phase I} + 22 \qquad (2)$$

Residual standard deviation = 9, $r = 0.90$.

Physiological deadspace

In 1938, Enghoff described the use of arterial $P\mathrm{CO_2}$ ($P\mathrm{a_{CO_2}}$) as a substitute for alveolar $\mathrm{CO_2}$ in equation (1); thus

$$V\mathrm{D^{phys}}/V\mathrm{T} = 1 - P\mathrm{E_{CO_2}}/P\mathrm{a_{CO_2}} \qquad (3)$$

where $V\mathrm{D^{phys}}$ is the physiological deadspace (partial pressure and fractions are interchangeable). The blood is now regarded as a "physiological integrator of the $\mathrm{CO_2}$ pressures existing in all parts of the lung" (Riley et al., 1946). $P\mathrm{a_{CO_2}}$ is the "ideal" $P\mathrm{A_{CO_2}}$ of a lung with perfect ventilation and perfusion. Apart from one drawback, that venous admixture gives rise to an apparent deadspace which is not a space, this change brought many advantages. In particular, it led to the realization that deadspace could exist in compartments other than the convective airways: the intrapulmonary, parallel (Folkow and Pappenheimer, 1955) or alveolar deadspace, $V\mathrm{D^{alv}}$ (Severinghaus and Stupfel, 1957). Thus

$$V\mathrm{D^{phys}} = V\mathrm{D^{aw}} + V\mathrm{D^{alv}} \qquad (4)$$

These compartments of V^{phys} can be illustrated as in figure 3, taken from Fletcher (1980), and based originally on Fowler (1948) and Nunn (1977). Here $V\mathrm{D^{aw}}$ is defined by the equal area method. A line representing $F\mathrm{a_{CO_2}}$, the $F\mathrm{CO_2}$ of a gas in equilibrium with arterial blood, allows the diagram to be divided into three parts. The area under the tracing, X, is the volume of $\mathrm{CO_2}$ in the breath and, therefore, represents effective ventilation. Areas Z and Y are defects in $\mathrm{CO_2}$ elimination representing wasted or deadspace ventilation attributable to $V\mathrm{D^{aw}}$ and $V\mathrm{D^{alv}}$, respectively. The difference between $F\mathrm{a_{CO_2}}$ and $F\mathrm{E'_{CO_2}}$, the arterial–end-tidal gradient, is variable in a given individual; it is reduced, for example, by increasing $V\mathrm{T}$ and decreasing frequency (Fletcher and Jonson, 1984), and increased by increasing alveolar pressure. The alveolar tidal volume, $V\mathrm{T^{alv}}$, is given in figure 3, as $V\mathrm{T} - V\mathrm{D^{aw}}$ (but observe that alveolar ventilation ($\dot{V}\mathrm{A}$) is not given by ($V\mathrm{T^{alv}}$ × frequency), because of the parallel existence of alveolar deadspace. ($V\mathrm{T^{alv}}$ × frequency)

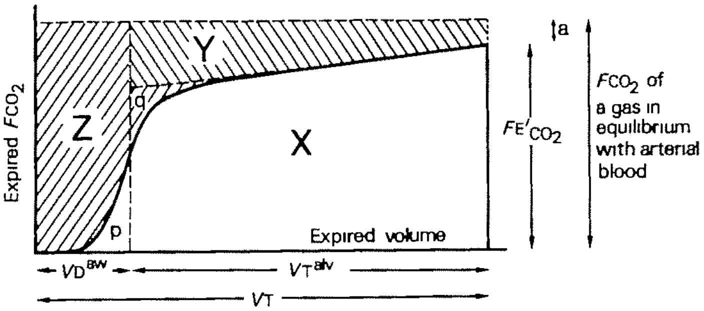

FIG. 3. Physiological deadspace and its subdivisions, modified from Fowler (1948) and Nunn (1977). Triangles p and q are of equal area. a = arterial–end-tidal $F\text{CO}_2$ difference.

describes the ventilation of *all* alveoli, regardless of their perfusion. The alveolar deadspace fraction is given by $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$, and the effectiveness of alveolar gas exchange is thus $1 - V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$.

A shortcoming of the graphical presentation shown in figure 3 is that we tend to imagine alveoli as either working perfectly ($F\text{A}_{\text{CO}_2} = F\text{a}_{\text{CO}_2}$) or not at all. Studies of ventilation/perfusion ($\dot{V}/\dot{Q}$) relationships show that there can exist both poorly perfused ($\dot{V}/\dot{Q} > 1$) and totally unperfused ($\dot{V}/\dot{Q} = \infty$) areas. Both types contribute to the alveolar deadspace we measure with SBT-CO_2.

Alveolar ventilation

Alveolar ventilation ($\dot{V}\text{A}$) is the total ventilation $\dot{V}\text{E}$ minus physiological deadspace ventilation, $\dot{V}\text{D}^{\text{phys}}$ (Otis, 1965).

$$\dot{V}\text{A} = \dot{V}\text{E} - \dot{V}\text{D}^{\text{phys}} \qquad (5)$$

Thus, it is a measure of the ventilation of alveoli with ideal ventilation and perfusion ($F\text{A}_{\text{CO}_2} = F\text{a}_{\text{CO}_2}$) and ignores alveolar deadspace ventilation. As an illustration of this concept, let us take the case of a pulmonary embolus in a previously healthy lung (fig. 4). Here, lung compartment B is unperfused, and has a ventilation of say 4 litre min^{-1}. Alveolar ventilation is that of perfused compartment A, also 4 litre min^{-1}; it is this ventilation which sustains the patient. To include ventilation of the unperfused compartment B in $\dot{V}\text{A}$ would be extremely misleading; this happens, however, if one attempts to calculate $\dot{V}\text{A}$ using $V\text{D}^{\text{Bohr}}$ (see below).

One of the problems with measuring $V\text{D}^{\text{aw}}$, which must be known in order to calculate $V\text{D}^{\text{alv}}$, (equation (4)) is that one must have the equipment to present SBT-CO_2. Hedenstierna and McCarthy (1975) examined nine "healthy" patients during anaesthesia/IPPV and found that the $V\text{D}$ obtained from end-tidal $F\text{CO}_2$ (that is, $V\text{D}^{\text{Bohr}}$) was very close to $V\text{D}^{\text{aw}}$. (There are two possible ways to do this. One can collect expired gas in a bag, whilst noting $F\text{E}'_{\text{CO}_2}$. The contents of the bag are then passed

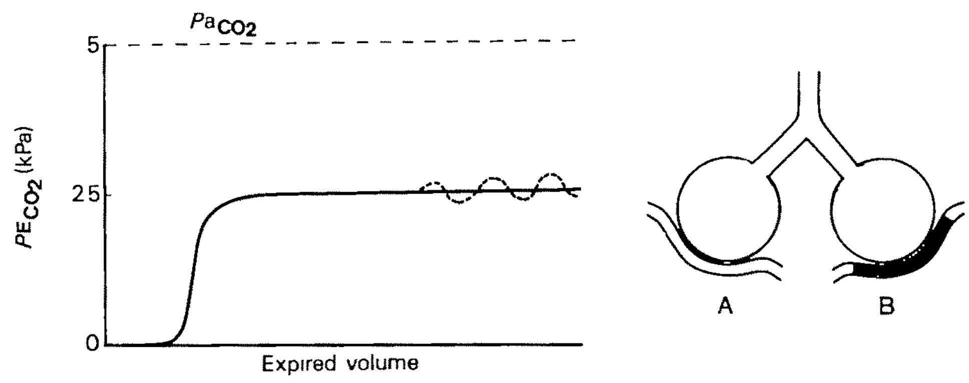

FIG. 4. Pulmonary embolism. Ventilation of unperfused lung B is alveolar deadspace ventilation. Only the perfused lung A performs alveolar ventilation. There is a large arterial–end-tidal CO_2 difference, approximately equal to $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ The diagram also shows cardiogenic oscillations in $P\text{E}_{\text{CO}_2}$ These are commonly seen when there are large intrapulmonary variations in $P\text{A}_{\text{CO}_2}$.

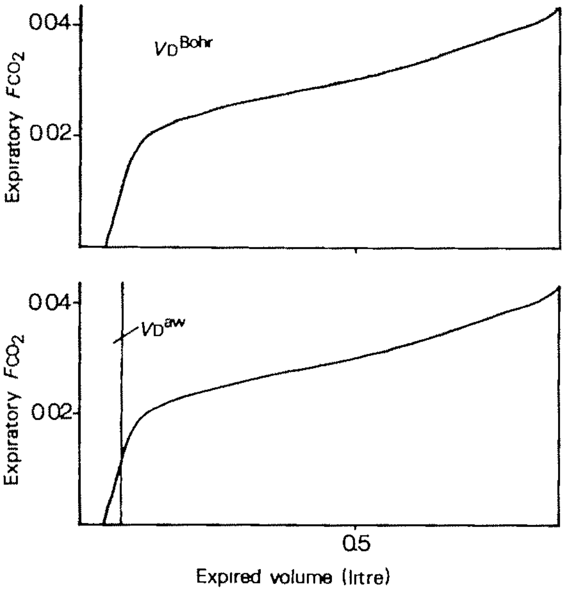

FIG 5 SBT-CO_2 obtained during anaesthesia/IPPV from 68-year-old male smoker. Upper tracing shows $V\mathrm{D}^{\mathrm{Bohr}}$ (272 ml)· lower shows $V\mathrm{D}^{\mathrm{aw}}$ (77 ml) at the same tidal volume of 840 ml. (Reproduced by permission of the editor of *Acta Anaesthesiol Scand.*)

through the CO_2 analyser to give $F\mathrm{E}_{\mathrm{CO}_2}$, correction being made for the change in $F\mathrm{CO}_2$ resulting from loss of water vapour at room temperature. In another method, using the CO_2 Analyzer 930, $F\mathrm{E}_{\mathrm{CO}_2}$ can be obtained from minute elimination of CO_2 divided by minute ventilation, after correcting for rebreathing in the Y-piece (Fletcher et al., 1983)). In some subsequent papers, $V\mathrm{D}^{\mathrm{Bohr}}$ has been regarded as a measure of $V\mathrm{D}^{\mathrm{aw}}$, and used to calculate $V\mathrm{D}^{\mathrm{alv}}$ from $V\mathrm{D}^{\mathrm{phys}}$ (Hedenstierna, 1975; Baehrendtz et al., 1983; Jonzon, Rondio and Sedin, 1983). However, reference to a "genuine" SBT-CO_2 (fig. 5) in comparison with Bohr's idealized one (fig. 1) shows that, whenever phase III slopes upwards, $V\mathrm{D}^{\mathrm{Bohr}}$ will exceed $V\mathrm{D}^{\mathrm{aw}}$, for the former includes a part of the alveolar deadspace. This is indeed the case in patients undergoing anaesthesia and artificial ventilation (Fletcher, 1984). The error in a typical anaesthetic population ($n = 58$) was of the order 25–120% (5th and 95th percentiles), and the magnitude of the error was, as predicted from theory, proportional to the slope of phase III, and greatest at large tidal volumes. Use of phase I (equation (2)) would appear to give a better estimate of $V\mathrm{D}^{\mathrm{aw}}$.

If $V\mathrm{D}^{\mathrm{Bohr}}$ is a poor estimate of $V\mathrm{D}^{\mathrm{aw}}$, is it ever a good estimate of $V\mathrm{D}^{\mathrm{phys}}$? From figures 3 and 5 it can be deduced that only when the arterial – end-tidal CO_2 gradient is zero will $V\mathrm{D}^{\mathrm{Bohr}}$ equal $V\mathrm{D}^{\mathrm{phys}}$. Most investigations of $P\mathrm{a}_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$ during anaesthesia (reviewed in Fletcher, 1980) show that this is not usually the case in adults during controlled or spontaneous ventilation, or even in children during spontaneous ventilation. However, $P\mathrm{a}_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$ is usually relatively small during controlled ventilation in children. Thus, $V\mathrm{D}^{\mathrm{Bohr}}$ approximates reliably to neither $V\mathrm{D}^{\mathrm{aw}}$ nor $V\mathrm{D}^{\mathrm{phys}}$, but is somewhere between them, except when phase III is completely horizontal or has a negative slope. Thus it cannot be used to calculate alveolar ventilation, since this requires knowledge of $V\mathrm{D}^{\mathrm{phys}}$. An estimate of alveolar ventilation based on $V\mathrm{D}^{\mathrm{Bohr}}$, let us call it $\dot{V}\mathrm{A}^{\mathrm{Bohr}}$, can be calculated from (minute elimination of CO_2/$F\mathrm{E}'_{\mathrm{CO}_2}$). It will usually be too large: in the example shown in figure 4, $\dot{V}\mathrm{A}^{\mathrm{Bohr}}$ is twice $\dot{V}\mathrm{A}$. However, in many situations such as paediatric anaesthesia (Evans, Hogg and Rosén, 1977; Lindahl, Hulse and Hatch, 1984), $\dot{V}\mathrm{A}^{\mathrm{Bohr}}$ may be the only measurement that is practicable. It is important that the uncertain relationship of $\dot{V}\mathrm{A}^{\mathrm{Bohr}}$ to $\dot{V}\mathrm{A}$ be borne in mind in these circumstances.

Use of end-tidal $P\mathrm{CO}_2$ *as an index of* $P\mathrm{a}_{\mathrm{CO}_2}$

During anaesthesia/IPPV there is an increased $P\mathrm{a}_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$ difference. In an investigation of 58 adults at tidal volumes of about 450 ml the median value was 0.6 kPa; the 5th and 95th percentiles were 0.2 and 1.4 kPa, respectively (Fletcher and Johnson, 1984). $P\mathrm{a}_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$ is least when phase III has only a slight slope, such as in young non-smokers, and increases when phase III slopes steeply, such as in lung disease. Because of the slope of phase III, $P\mathrm{a}_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$ decreases as $V\mathrm{T}$ is increased.

Changes in end-tidal $P\mathrm{CO}_2$ can often be regarded as indicative of changes in $P\mathrm{a}_{\mathrm{CO}_2}$. $P\mathrm{E}'_{\mathrm{CO}_2}$ is especially useful if its relationship to $P\mathrm{a}_{\mathrm{CO}_2}$ can be established initially by blood-gas sampling, so that changes in $P\mathrm{a}_{\mathrm{CO}_2}$ thereafter may be assumed to occur roughly in parallel. However, variations in $P\mathrm{a}_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$ during major surgery may be of the same magnitude as the interindividual variation in $P\mathrm{a}_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$ (Raemer et al., 1983). Operative procedures such as sternotomy or thoracotomy, extracorporeal circulation, and aortic clamping are all likely to change $\dot{V}/\dot{Q}$ relationships, the alveolar deadspace fraction and, thus, $P\mathrm{a}_{\mathrm{CO}_2} - P\mathrm{E}'_{\mathrm{CO}_2}$. It may be expected that, in severe lung disease, changing the ventilatory pattern, for example from volume-controlled to pressure-controlled ventilation, will have far-reaching effects on the efficiency of gas exchange, and therefore on the Pa_{CO_2} – $P\mathrm{E}'_{CO_2}$ relationship. Changes in $Pa_{CO_2} - P\mathrm{E}'_{CO_2}$ may occur during operation in the carcinoid syndrome (Fletcher et al., 1981), during pulmonary embolism and during hypotension. In these cases the change mirrors those in $V\mathrm{D}^{\mathrm{alv}}/V\mathrm{T}^{\mathrm{alv}}$.

CONCLUSION

There are two ways of measuring the respiratory deadspace: one is with use of arterial $P\mathrm{CO}_2$, giving $V\mathrm{D}^{\mathrm{phys}}$ and, if $V\mathrm{D}^{\mathrm{aw}}$ can be determined, $V\mathrm{D}^{\mathrm{alv}}$. This is "invasive" deadspace measurement, and it allows us to calculate alveolar ventilation ($\dot{V}\mathrm{A}$) the life-sustaining ventilation of perfused alveoli. Without measurement of blood-gas tensions, we have a "non-invasive" deadspace, $V\mathrm{D}^{\mathrm{Bohr}}$, which is greater than $V\mathrm{D}^{\mathrm{aw}}$, but less than $V\mathrm{D}^{\mathrm{phys}}$. Similarly, $\dot{V}\mathrm{A}^{\mathrm{Bohr}}$ is greater than $\dot{V}\mathrm{A}$ and less than the ventilation of *all* alveoli, perfused and unperfused. For reasons discussed in the text, deductions about $V\mathrm{D}^{\mathrm{alv}}$ or $\dot{V}\mathrm{A}$ cannot be made from "non-invasive" deadspace measurements. $V\mathrm{D}^{\mathrm{aw}}$ (or phase I) may of course be measured "non-invasively". The use of $P\mathrm{E}'_{CO_2}$ as an index of Pa_{CO_2} is limited, especially in older subjects, by the large inter-individual variation and is most valuable when the Pa_{CO_2} – $P\mathrm{E}'_{CO_2}$ difference can initially be established by measurement of blood-gas tensions, but even this may be unreliable during major surgery. Non-invasive methods have an important role to play in clinical monitoring and scientific studies, but it is important to understand their limitations.

Roger Fletcher

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FENTANYL BY CONSTANT RATE I.V. INFUSION FOR POSTOPERATIVE ANALGESIA

W. S. NIMMO AND J. G. TODD

SUMMARY

Fentanyl by continuous i.v. infusio ($1.5\ \mu g\ kg^{-1}\ min^{-1}$ or $0.5\ \mu g\ kg^{-1}\ min^{-1}$) wa compared with placebo infusion as an analges regimen for 24 h after hysterectomy. The drug were infused using a new disposable device whic required no external power source. All patien were allowed morphine i.m. if they experience pain. Patients in the higher dose fentanyl grou demanded less i.m. morphine and had better pai relief after operation, without important respirato depression.

Fentanyl is a synthetic opioid analgesic 50 times more potent than morphine, with a more rapid onset and shorter duration of effect (Romagnoli, 1973). The drug has been administered by i.v. infusion during anaesthesia and for short periods thereafter (McQuay et al., 1979; Hengstmann, Stoeckel and Schuttler, 1980), but there is little information concerning attempts to prevent the onset of postoperative pain by infusing fentanyl i.v. for 24 h.

Accurate infusion of drugs for 24 h usually requires a mechanical or electrical syringe driver or pump, and it is likely that this has reduced the popularity of this approach. We report a 24-h infusion study using a disposable infusion device requiring no external power source—the Baxter Travenol Infusor.

THE BAXTER TRAVENOL INFUSOR

The infusor (fig. 1) (Ausman et al., 1982) consists of an elastomeric balloon which is distended by the operator filling it with 60 ml of the desired solution; the distension of the balloon provides the pressure for infusion. This pressure is in excess of 620 mm Hg and the infusion will continue even if the i.v. cannula is kinked or comes out of the vein and enters the tissues. The device is designed to run for 24 h, a flow restrictor within it regulating the rate of infusion to 2 ml h^{-1}. The 12 ml of infusion that remains within the device after this time is a reserve and should be discarded.

The accuracy of the device depends on the viscosity of the solution and the manufacturers recommend that 5% dextrose is used as the diluent. Throughout our study, regular observations of the volume left in the infusor were made and no devi tion from the predicted infusion rate was recorded

PATIENTS AND METHODS

Twenty-four women undergoing elective hysterectomy through a transverse abdominal incision wer studied on consecutive operating lists of one consultant gynaecologist. Informed consent and ethic committee approval were obtained.

The patients were allocated randomly to thre groups to receive one of three infusion regimens:

(1) Fentanyl $1.5\ \mu g\ kg^{-1}\ h^{-1}$ (nine patients)
(2) Fentanyl $0.5\ \mu g\ kg^{-1}\ h^{-1}$ (eight patients)
(3) Placebo infusion of 5% dextrose (seve patients)

The infusion was instituted 1–2 h before inductio of anaesthesia. Premedication was with atropin 0.6 mg i.m. After induction of anaesthesia wit thiopentone 3–5 mg kg^{-1} and neuromuscular blo kade, the trachea was intubated and the lungs we ventilated with 67% nitrous oxide and 1% halotha or enflurane in oxygen. A bolus dose of fentan 100 µg was given i.v. At the end of anaesthesia, eac patient was prescribed Cyclimorph (morphi 10 mg and cyclizine 50 mg) i.m., to be given

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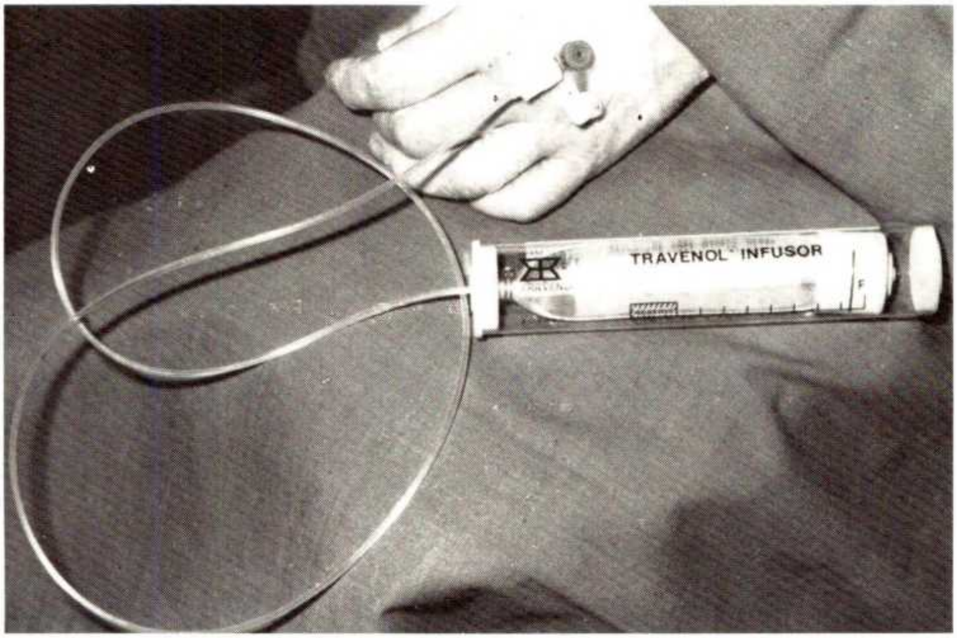

FIG. 1. The Baxter Travenol Infusor. The device is filled with the calculated amount of fentanyl diluted in 5% dextrose to a volume of 60 ml. It administers 2 ml h^{-1} for 24 h. The reserve is then discarded.

demand at the discretion of the recovery room nurse.

All operations were carried out by one surgeon, and anaesthesia was carried out by one of two anaesthetists. All assessments were carried out by an anaesthetist not otherwise involved in the care of the patient. The patient, surgeon, recovery room nurses and the assessor for the study were unaware of which infusion had been administered.

The following assessments and observations were made by the assessor in the period after operation, at 4, 8, 12 and 24 h after the start of the infusion:

(1) Pain scores. Pain was graded as none, mild, moderate or severe.

(2) Conscious level.

(3) Respiratory rate.

(4) Heart rate.

(5) Arterial pressure.

(6) Peak respiratory flow using a Wright mini-peak flow meter. The best of three attempts was expressed as a percentage of the value before operation.

(7) Nausea or vomiting.

(8) The number of doses of Cyclimorph administered.

All observations were made with the patient semi-recumbent in bed. Arterial blood-gas tensions were measured at 12 and 24 h. Plasma fentanyl concentrations were measured by radioimmunoassay at 12 and 24 h (Michiels, Hendriks and Heykants, 1977). An overall assessment of pain was made by the patient and by the observer at 24 h.

Statistical analysis was by analysis of variance, Mann–Whitney U test or Fisher's exact probability test.

RESULTS

Patient data are given in table I. There were no significant differences between the groups.

Pain assessment

Patients receiving the more concentrated infusion of fentanyl demanded significantly fewer doses of Cyclimorph than those in the placebo group ($P < 0.05$) (table II).

Compared with patients receiving placebo (18 of 28 observations of moderate to severe pain), both groups receiving fentanyl had a statistically significant reduction in the frequency of moderate to severe pain after surgery, the more concentrated infusion giving greater relief (fentanyl 1.5 $\mu g\ kg^{-1}\ h^{-1}$: 7 of 36 observations were of moderate to severe pain ($P < 0.01$ compared with placebo); fentanyl

TABLE I. *Patient data (mean ± SD)*

Group	n	Age (yr)	Weight (kg)	Duration of surgery (min)
Fentanyl $1.5\ \mu g\ kg^{-1}\ h^{-1}$	9	36 ± 7	57.6 ± 5.5	76 ± 19
Fentanyl $0.5\ \mu g\ kg^{-1}\ h^{-1}$	8	37 ± 10	59.4 ± 10.2	69 ± 20
Placebo	7	48 ± 15	57.6 ± 5.5	67 ± 7

$0.5\ \mu g\ kg^{-1}\ h^{-1}$: 12 of 20 observations were of moderate to severe pain ($P < 0.05$)).

Independent patient and observer assessments of the overall pain experienced in the 24 h were in complete agreement, and are shown in table II. Both fentanyl groups experienced significantly less pain than the placebo group, but relief was statistically greater with fentanyl $1.5\ \mu g\ kg^{-1}\ h^{-1}$ ($P < 0.01$) than with $0.5\ \mu g\ kg^{-1}\ h^{-1}$ ($P < 0.05$).

Respiratory effects

There was no evidence of important respiratory depression in any of the groups (table III). In four patients the respiratory rate decreased to less than 12 b.p.m. once in the 24 h, but it was never less than 8 b.p.m. These patients were all in the high-dose fentanyl group, and the group as a whole had respiratory rates at 12 and 24 h which were significantly less than those of patients in the placebo group.

In only two patients (one in the placebo group and one in the high-dose fentanyl group) did arterial carbon dioxide tension reach a value greater than 5.87 kPa (44 mm Hg) (6.27 kPa (47 mm Hg) in each). There were no statistically significant differences between the groups in the arterial blood-gas tensions of oxygen or carbon dioxide at 12 and 24 h (table III).

There was a significant difference between the groups in the number of observations of greater than 50% of the preoperative peak expiratory flow (table III), compatible with the improved analgesia in the group receiving fentanyl $1.5\ \mu g\ kg^{-1}\ h^{-1}$. The mean peak expiratory flow at 12 h was 62%, 61% and 46% of the preoperative value in the fentanyl $1.5\ \mu g\ kg^{-1}\ h^{-1}$, fentanyl $0.5\ \mu g\ kg^{-1}\ h^{-1}$ and placebo groups, respectively.

Other observations

Throughout the study, there were no important changes in heart rate, arterial pressure or level of consciousness. In particular, all patients remained conscious and orientated throughout. There was a high incidence of vomiting in all three groups, but no significant difference between them: six patients in the fentanyl $1.5\ \mu g\ kg^{-1}\ h^{-1}$, four in the fentanyl $0.5\ \mu g\ kg^{-1}\ h^{-1}$ and three in the placebo groups, respectively, vomited.

Plasma fentanyl concentrations

The mean plasma fentanyl concentrations are shown in table IV. There were no statistically significant within-group differences between the concentrations at 12 and 24 h in the two groups who received fentanyl. Assuming the concentration at 24 h represented a steady state concentration, the mean fentanyl clearance was 17.0 ± 5.6 ml $kg^{-1}\ min^{-1}$ (± SD) in the fentanyl $0.5\ \mu g\ kg^{-1}\ h^{-1}$ infusion and 17.0 ± 9.2 ml $kg^{-1}\ min^{-1}$ in the fentanyl $1.5\ \mu g\ kg^{-1}\ h^{-1}$ infusion.

TABLE II. *Pain assessment. Compared with placebo:* *$P<0.05$; **$P<0.01$

Group	Doses of Cyclimorph (mean ± SD)	Pain: no. observations None–mild	Pain: no. observations Moderate–severe	24-h assessment of pain None–mild	24-h assessment of pain Moderate–severe
Fentanyl $1.5\ \mu g\ kg^{-1}\ h^{-1}$	2.0 ± 0.7*	29	7**	8	1**
Fentanyl $0.5\ \mu g\ kg^{-1}\ h^{-1}$	2.6 ± 1.6	20	12*	4	4*
Placebo	3.6 ± 0.8	10	18	0	7

TABLE III. *Respiration (mean ± SD). Compared with placebo:* *P<*0.05*; **P<*0.01*

Group	Resp. rate (b.p.m.)		$P\text{O}_2$ (kPa)		$P\text{CO}_2$ (kI		Peak expiratory flow: no. of observations	
	12 h	24 h	12 h	24 h	12 h	24 h	<50% normal	>50% normal
Fentanyl 1.5 μg kg^{-1} h^{-1}	14 ± 3*	15 ± 4*	10.8 ±1.3	10.3 ±0.9	5.5 ±0.5	5.3 ±0.5	12	24**
Fentanyl 0.5 μg kg^{-1} h^{-1}	19 ± 2	18 ± 2	10.4 ±0.8	9.6 ±1.5	5.2 ±0.5	5.2 ±0.4	13	19*
Placebo	21 ± 1	19 ± 1	11.5 ±0.9	11.1 ±0.9	4.8 ±0.6	4.9 ±0.6	20	8

DISCUSSION

Infusion of fentanyl 1.5 μg kg^{-1} h^{-1} for 24 h produced satisfactory postoperative analgesia without important respiratory depression. Patients receiving this regimen had less pain, better peak expiratory flow measurements and demanded less additional prescribed opioids. An infusion regimen of 0.5 μg kg^{-1} h^{-1} did not differ markedly from placebo, although the pain relief was significantly better.

The regimen was designed so that fentanyl infusion began 1–2 h before surgery and a bolus dose of 100 μg was given during anaesthesia in the hope that plasma concentrations would approximate to the "analgesic" steady state concentrations when the patients recovered from anaesthesia. Other studies, in which opioid infusions have been established after surgery, have experienced early failure of analgesia or have included a bolus dose of opioid in the recovery room (Stapleton, Austin and Mather, 1979; Rutter, Murphy and Dudley, 1980). However, patients in the group receiving fentanyl 1.5 μg kg^{-1} h^{-1} received a larger combined total dose of opioid agents than the placebo group, in spite of the fact that the latter group demanded more doses of Cyclimorph. This smaller dosage in our placebo group is compatible with previous studies that have suggested that patients prescribed i.m. pulsed doses of opioid analgesia "on demand" receive too little drug in the period after operation (Hug, 1980; Hull and Sibbald, 1981).

TABLE IV. *Plasma fentanyl concentrations (ng ml^{-1}) (mean ± SD)*

Group	12 h	24 h
Fentanyl 1.5 μg kg^{-1} h^{-1}	1.62 ± 0.27	1.79 ± 0.67
Fentanyl 0.5 μg kg^{-1} h^{-1}	0.61 ± 0.32	0.56 ± 0.25

The clearance of fentanyl described in this study (17 ml kg^{-1}min^{-1}) is not very different from that reported after a single i.v. dose in volunteers (13.3 ml kg^{-1}min^{-1}) (McClain and Hug, 1980).

The use of disposable infusors might make this type of provision of analgesia easier for patients and nursing staff. The device itself is quite expensive and requires that some drug is discarded after 24 h. The high pressure within the balloon means that the infusion will not stop if the catheter leaves the vein and enters the tissues. Little is known of prolonged infusion of fentanyl to the tissues. However, this method of delivering analgesia seems worthy of study in other types of postoperative pain. It improves pain relief and avoids the high capital investment and maintenance costs of conventional electrical infusion pumps.

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COMPARISON OF INFUSIONS OF MORPHINE AND LYSINE ACETYL SALICYLATE FOR THE RELIEF OF PAIN AFTER SURGERY

J. N. CASHMAN, R. M. JONES, J. M. G. FOSTER AND A. P. ADAMS

SUMMARY

The effect of a constant i.v. infusion of lysine acetyl salicylate (LAS) on pain after operation was compared with that of a constant infusion of morphine in 30 patients undergoing unilateral inguinal herniorrhaphy. LAS provided analgesia equivalent to that provided by morphine and was associated with significantly less drowsiness, nausea and vomiting. No patient in either group was noted to suffer from respiratory depression. No untoward side effects were noted during or following the administration of LAS.

Lysine acetyl salicylate (LAS) is a water soluble salt of acetylsalicylic acid which may be given parenterally (LAS 1.8 g is equivalent to acetylsalicylic acid 1 g). The results of previous studies with LAS have been conflicting: some investigators suggest that its analgesic efficacy is comparable to that of opioids (Kweekel-De Vries et al., 1974; Blendinger and Eberlein, 1980; Korttila, Pentti and Auvinen, 1980), while others believe that, although LAS has some analgesic effect, it may not be comparable to opioids (McAteer and Dundee, 1981).

We are unaware of any previous studies which have used a constant i.v. infusion of LAS to provide analgesia after surgery. A double-blind comparison of the effectiveness of an infusion of LAS with an infusion of morphine has been undertaken following unilateral inguinal herniorrhaphy.

PATIENTS AND METHODS

Thirty patients (ASA class I/II) undergoing elective repair of an unilateral inguinal hernia were studied. The study was approved by the local ethics advisory committee and written informed consent obtained from each patient. Patients with a known intolerance or sensitivity to salicylates, an abnormal bleeding tendency or with a past history of peptic ulceration were excluded. Bleeding times were estimated in all patients before surgery. The patients were allocated randomly to one of two treatment groups to receive either LAS or morphine. The trial was conducted double-blind, with all assessments of pain being made by a single observer. A five-point verbal pain scoring system was used to grade the intensity of pain: none = 0; mild = 1; moderate = 2; severe = 3; very severe = 4 (Dundee, 1980). Analogue rating scales were used to assess the following side effects in the period after operation: drowsiness, dizziness, nausea, vomiting and sweating.

Anaesthesia was standardized in both groups. Premedication was with diazepam 10 mg orally and atropine 0.6 mg i.m. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and maintained with halothane and nitrous oxide in oxygen (2:1).

The severity of pain was assessed immediately the patients arrived in the recovery area. Patients were then allocated randomly to receive an initial bolus dose of either morphine 10 mg i.v. or LAS 1.8 g i.v., administered over 5 min. Subsequent assessments of the severity of pain were made at 30 min and at 3 h; a constant rate i.v. infusion was then commenced, so that patients received a further dose of either morphine 40 mg or LAS 7.2 g over the following 24 h. Further assessments of pain were made after the infusion had been in progress for 3 h, 18 h and on completion of the infusion. Patients were asked to indicate their overall assessment of pain at the end of the 24-h infusion period. Papaveretum

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10–15 mg i.m. was prescribed as rescue analgesia.

In a pilot study, the analgesic requirements of 10 patients undergoing unilateral inguinal herniorrhaphy were assessed. All of these patients were prescribed opioid analgesia to be administered as required. We found that seven patients received an analgesic at some time after surgery, and that of the three who did not, all had received an opioid as part of their pre-anaesthetic medication. In view of this, a placebo group was not included in the present study.

Results are expressed as mean (SD). Comparison between the groups has been made using the unpaired Student's *t* test. Pain scores were analysed statistically using the Mann–Whitney *U* test for non-parametric data. The incidence of side effects was compared using the chi-squared test with Yates' correction factor. Values of $P < 0.05$ were considered statistically significant.

RESULTS

The two groups were comparable with regard to age, weight and duration of surgery (table I). No patient had a bleeding time before surgery greater than 240 s.

The results are represented graphically in figures 1 and 2.

The mean pain scores did not differ significantly at any time. The mean pain scores when the patients arrived in the recovery area were 1.47 in the LAS group and 1.60 in the group who received morphine. Either analgesic agent effected a significant decrease in the severity of pain after 30 min (0.93 LAS group and 0.80 morphine group), but after 3 h the pain scores had increased (1.73 LAS group and 1.53 morphine group). After the infusion had been in progress for 3 h, the pain scores had again decreased significantly (0.53 LAS group and 0.67 morphine group), and remained low at 18 h (0.13 LAS group and 0.20 morphine group) and on completion of the infusion (0.07 LAS group and 0.20 morphine group). There was no difference in the patients' overall assessment of pain during the period of the investigation (0.67 LAS group and 0.77 morphine group).

TABLE I. *Patient data (mean (SD))*

Treatment group	Age (yr)	Weight (kg)	Duration of surgery (min)
LAS ($n = 15$)	52.5 (14.8)	75.3 (9.9)	49.6 (19.0)
Morphine ($n = 15$)	49.3 (14.4)	74.1 (10.5)	47.7 (13.3)

Two patients in the LAS group required papaveretum i.m., one of them twice. Two patients in the morphine group received papaveretum i.m., one of them more than twice. Three patients in the LAS group complained of mild nausea, one of whom vomited, as did one other patient in this group. Eleven patients in the morphine group complained of nausea, which was mild in eight and of moderate severity in three; three of these 11 patients experienced vomiting. This difference between the two groups was significant ($P < 0.05$). One patient in the

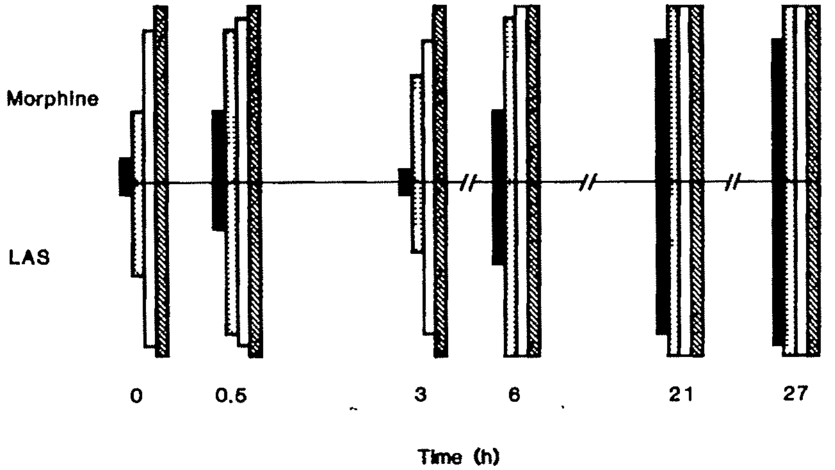

FIG 1. Cumulative frequency histogram of the pain scores in the two groups. Black columns = no pain; dotted columns = no or mild pain; open columns = no, mild or moderate pain; cross-hatched columns = no, mild, moderate or severe pain.

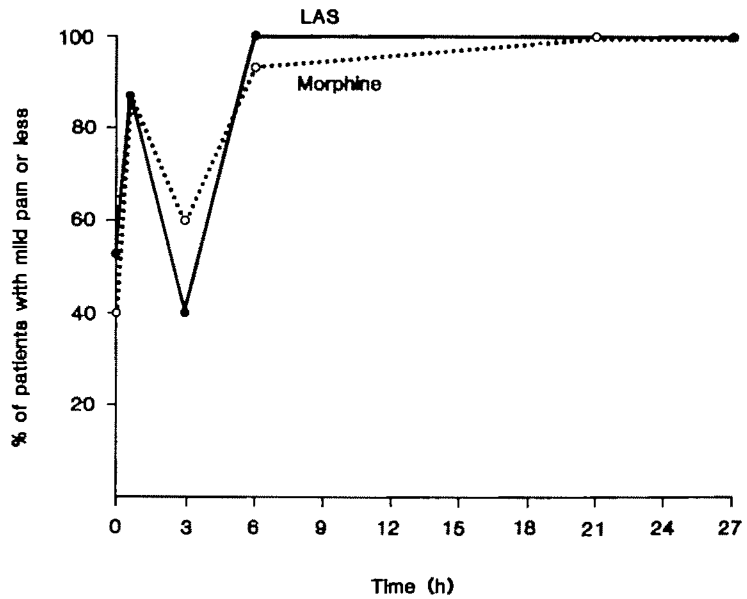

FIG 2. Comparison of the percentage of patients within each group with no pain or mild pain only.

LAS group and eight patients in the morphine group complained of drowsiness ($P < 0.05$). Furthermore, all of the patients in the LAS group were assessed by the observer as being awake and alert during the infusion, while seven of the patients in the morphine group were rated as being drowsy at some stage during the infusion ($P < 0.01$). No patient in either group was noted to suffer from respiratory depression.

DISCUSSION

Morphine and other opioid analgesics are used commonly to provide analgesia after surgery. However, there are several undoubted disadvantages associated with their use (Editorial, 1978). These include respiratory depression, nausea and vomiting. Other considerations include drowsiness—which may or may not be a disadvantage, depending upon its degree—as well as legislative restrictions and the possibility, albeit remote, of drug dependence. Non-opioids, such as the salicylates, have the advantage of being free from these side effects and have much to commend their use, provided that the analgesia produced is comparable to that of the opioids (Editorial, 1980).

There have been few controlled studies of LAS for the relief of pain after surgery. LAS has been investigated when given i.m. (Kweekel-De Vries et al., 1974; Korttila, Pentti and Auvinen, 1980), and when given as a bolus i.v. (Blendinger and Eberlein, 1980; Tammisto and Tigerstedt, 1980; McAteer and Dundee, 1981). The results of these studies have been inconclusive with regard to the relative merit of LAS compared with opioid analgesics. Furthermore, intraoperative opioids were used in some of these studies (Kweekel-De Vries et al., 1974; McAteer and Dundee, 1981), and in one study LAS was not administered until at least 16 h after surgery (Blendinger and Eberlein, 1980).

Intermittent injections of analgesics i.m., even when carried out at strictly regular intervals may be associated with poor control of pain after operation (Editorial, 1978; Austin, Stapleton and Mather, 1980a). This may be the result of variability in rates of absorption resulting in widely fluctuating and unpredictable blood concentrations of analgesic (Mather et al., 1975; Shih, Robinson and Au, 1976; Editorial, 1978). Indeed, it has been suggested that there is a minimum analgesic concentration necessary for effective pain relief (Shih, Robinson and Au, 1976; Austin, Stapleton and Mather, 1980b). The administration of an analgesic in small but frequent doses or as an infusion results in a more stable blood concentration and may be expected to provide superior analgesia (White, 1982).

The results of the present study suggest that, after inguinal herniorrhaphy, an i.v. infusion of LAS provides pain relief of a quality similar to that provided by morphine—a conclusion in broad agreement with that of a number of other workers (Kweekel-De Vries et al., 1974; Blendinger and Eberlein, 1980; Korttila, Pentti and Auvinen, 1980; Tammisto and Tigerstedt, 1980; McAteer and Dundee, 1981). However, reservations have been expressed concerning the efficacy of LAS in the treatment of pain after surgery, and it has been suggested that its use be reserved until the later postoperative period (McAteer and Dundee, 1981) or alternatively that, if it is used in the period immediately after operation, it be supplemented with a small dose of opioid (Tammisto and Tigerstedt, 1980). In one study, LAS was found to have a significantly slower onset of action than oxycodone; this was felt to be consistent with its pharmacokinetic properties (Korttila, Pentti and Auvinen, 1980), since LAS must first be converted to acetyl salicylate, which is then metabolized in the liver to salicylic acid (the active form of the drug). It is salicylic acid which reduces the sensitivity of pain receptors to nociceptive stimuli by decreasing prostaglandin synthesis (Vane, 1971). Previous studies have tended to wait for the patients to complain of pain before administering any analgesic and this has been, on average, 60 min after the end of surgery. This may offer a partial explanation for some of the conflicting results. We decided to administer the trial drug as soon as the patients regained consciousness, rather than wait for the complaint of pain.

The lower incidence of side effects associated with LAS was confirmed. Although we did not measure bleeding times during the infusion period, nor make any comparison of blood loss between the two groups, results from a similar trial in patients undergoing thoracic surgery suggest that LAS is not associated with a significantly greater blood loss after surgery than is morphine (Jones et al., 1985). Indeed, although small doses (<1 g) of aspirin prolong bleeding time, the drug appears to have a paradoxical effect in that there is no significant prolongation if larger doses (>1 g) are used (O'Grady and Moncada, 1978; Rajah, Penny and Kester, 1978).

In conclusion, following inguinal hernia repair, infusion of LAS i.v. can provide pain relief equivalent to that provided by the i.v. infusion of morphine and is associated with a significantly lower incidence of nausea, vomiting and drowsiness.

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COMPARISON OF INFUSIONS OF MORPHINE AND LYSINE ACETYL SALICYLATE FOR THE RELIEF OF PAIN FOLLOWING THORACIC SURGERY

R. M. JONES, J. N. CASHMAN, J. M. G. FOSTER, J. R. WEDLEY AND A. P. ADAMS

SUMMARY

A double-blind study comparing the effectiveness of a continuous infusion i.v. of lysine acetyl salicylate (LAS) with an infusion of morphine for the treatment of pain following pulmonary surgery is described. Mean pain scores in the two groups were not significantly different at any stage during the 24-h period of study. LAS was not associated with any significantly greater blood loss in the period after operation. The incidence of drowsiness, nausea and vomiting, and the need for anti-emetic medication were similar in both groups.

The parenteral administration of potent analgesic agents, most commonly of the narcotic group, remains the principal form of treatment for postoperative pain. However, narcotic analgesics may produce undesirable side effects: drowsiness, emesis and respiratory depression. Moreover, their use is subject to legislative restrictions. Hitherto, the availability of parenteral preparations of non-narcotic analgesics has been limited. However, it has been suggested that a parenteral salicylate preparation, lysine acetyl salicylate (LAS), in a dose of 1.8 g (equivalent to acetyl salicylate 1 g), can provide analgesia equivalent to that provided by morphine 10 mg (Kweekel-De Vries et al., 1974). This study reports on a comparison of the analgesic effect of a continuous i.v. infusion of LAS with that of morphine (administered similarly) for the relief of pain following thoracotomy.

PATIENTS AND METHODS

The study was approved by the hospital ethics committee and 22 patients gave written informed consent. All patients were ASA class II/III, aged between 28 yr and 77 yr and scheduled to undergo a standard thoracotomy for pulmonary surgery. The patients were randomly allocated to two groups to receive either LAS or morphine. The trial was conducted double-blind and one of the authors (JC) carried out all of the pain assessments using a simple verbal 5-point scoring system (none = 0; mild = 1; moderate = 2; severe =3; very severe = 4). Bleeding times and platelet counts were estimated before operation in all patients. Patients with a known intolerance to salicylates, with an abnormal bleeding tendency or prolonged bleeding time, or with a history of peptic ulceration were excluded from the trial.

Patients were premedicated with diazepam 10 mg by mouth and atropine 0.6 mg i.m. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and pancuronium 0.07 mg kg^{-1} was administered to facilitate endobronchial intubation. Anaesthesia was maintained with nitrous oxide in oxygen supplemented with 0.5–1.0% halothane. Intercostal blockade was not performed, nor was cryotherapy used. All of the operations were performed by the same surgeon.

At the termination of surgery all patients received a single injection of papaveretum 10 mg i.m.; residual neuromuscular blockade was antagonized with neostigmine 2.5 mg (plus atropine 1.2 mg) and the patient was returned to the recovery area when the anaesthetist was satisfied with the patient's haemodynamic and respiratory status. After surgery, assessments of the severity of the pain were made by one single-blinded observer. The initial pain assessment was not made until the patient had recovered sufficiently from the anaesthetic to com-

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municate a verbal pain score. Following the initial assessment of pain in the recovery area, patients were allocated randomly to receive either morphine 10 mg or LAS 1.8 g administered i.v. over 5 min. Pain assessments were then made 30 min and 1 h after the initial dose of the trial drug. After the latter assessment a 24-h i.v. infusion administering a total dose of either morphine 40 mg or LAS 7.2 g was commenced. Subsequent assessments were made after the infusion had been in progress for 3 and 18 h, and on completion of the infusion, at which time the patients were asked for an overall assessment of pain.

During the 24-h infusion, patients were able to self-administer a preset incremental dose of papaveretum 0.5 mg i.v., delivered over 1 min, from an automatic patient-controlled analgesic (PCA) device, with the lockout time set at 60 min (Cardiff Palliator). The cumulative dose administered by this device was recorded after 3, 18 and 24 h. Papaveretum 10–15 mg i.m. was prescribed for any patient who required further pain relief. Analogue rating scales were used to assess the possible side effects of drowsiness, nausea and vomiting during the period after operation. A record of respiratory rate was made every 10 min for the first hour, every 15 min for the next hour, every 30 min for the next 2 h, every 60 min for the next 8 h, 2-hourly for the following 8 h and 4-hourly thereafter. An assessment of postoperative bleeding was made by measuring the daily loss recovered via the intercostal drains, for as long as these remained *in situ*.

Statistical analysis of data

Student's *t* test (unpaired) was used for between-group comparisons of demographic data; pain scores and other non-parametric data were analysed using the Wilcoxon's ranking test for unpaired data. A comparison of the incidence of side effects was made using the Chi-squared test with the Yates' correction factor. Values of $P < 0.05$ were considered to be statistically significant. All results are reported as mean (standard deviation).

TABLE I. *Demographic data*

	Age (yr)	Weight (kg)	Sex ratio
Morphine group (n=10)	56.4 (13 8)	67.3 (12.5)	8M/2F
LAS group (n=10)	61.5 (6.9)	63.9 (6.3)	7M/3F
P	ns	ns	

RESULTS

Treatment groups

There were no significant differences in age, sex distribution, body weight or type and duration of surgery between the two groups (tables I and II). No patient had a preoperative bleeding time of greater than 240 s. Two patients were withdrawn from the trial as a result of violations of procedure, thus 20 patients were studied, 10 who had received morphine and 10 who received LAS. One patient in the LAS group received a small dose of fentanyl (100 μg) during the operation.

Evaluation of pain

The mean pain scores are outlined in table III. On arrival of the patient in the recovery area, the mean pain scores were 2.70 and 2.45 for the LAS and morphine groups, respectively (ns). The mean pain scores of the two groups did not differ significantly at any time (although initially the scores were slightly lower in the morphine group). The use of patient controlled analgesia (PCA) was not significantly different in the two groups (table IV). Adjusted to a μg kg^{-1} h^{-1} basis, the LAS group self-administered overall papaveretum 4.4 μg kg^{-1} h^{-1} and the morphine group 3.7 μg kg^{-1} h^{-1}. Additional analgesia i.m. was required by two patients in the LAS group and by three patients in the morphine group. All patients were satisfied with the overall quality of pain relief (overall mean pain scores: LAS 1.60 and morphine 1.80). The mean time from completion of the 24-h infusion to the first subsequent administration of an analgesic was 4.54 (2.60) h in the LAS group and 3.01 (2.09) h in the morphine group (ns).

TABLE II. *Details of surgery. *Removal of aspergilloma (one in morphine group, two in LAS group); decortication of lung (one in morphine group)*

	Duration (min)	Pneumonectomy	Lobectomy	"Open & close"	Other*
Morphine group	132.0 (42.3)	0	6	2	2
LAS Group	139.5 (41.3)	2	5	1	2
P	ns				

TABLE III. *Mean pain scores during the period of study*

	Time from commencement of infusion (h)						
	−1	−0.5	0	3	18	24	Overall
Morphine group	2.45	2.40	2.25	1.55	0.70	0.55	1.80
LAS group	2.70	2.90	2.70	1.90	0.60	0.20	1.60
P	ns	ns	ns	ns	ns	ns	ns

TABLE IV. *Use of PCA — mean dose (mg) of papaveretum self-administered*

	Time from commencement of infusion (h)		
	3	18	24
Morphine group	1.55 (0.35)	4.80 (2.20)	6.05 (2.73)
LAS group	1.80 (0.35)	5.50 (1.89)	6.75 (1.77)
P	ns	ns	ns

TABLE V. *Incidence of side effects*

	Patients with nausea	Patients vomiting	Patients requiring anti-emetic
Morphine group	2	2	3
LAS group	4	2	3

TABLE VI. *Mean sedation scores for the two treatment groups*

	Time from commencement of infusion (h)				
	−0.5	0	3	18	24
Morphine group	2.5 (0.71)	2.3 (0.67)	1.8 (0.63)	1.3 (0.48)	1.2 (0.42)
LAS group	2.1 (0.99)	1.6 (0.52)	1.4 (0.52)	1.0 (0.0)	1.0 (0.0)
P	ns	<0.01	ns	ns	ns

Side effects

There were no differences in the incidence of nausea, vomiting or use of anti-emetics between the two groups (table V). Morphine was associated with higher sedation scores throughout (table VI), although this difference was significant only at 1 h. No patient in either group was noted to have a respiratory rate of less than 12 b.p.m. at any stage. The mean daily blood loss collected from the intercostal drains was 251 ml in the LAS group (range 122–491 ml) and 213 ml in the morphine group (range 90–462 ml); this difference was not significant.

DISCUSSION

Stapleton, Austin and Mather (1979) have suggested that a continuous i.v. infusion of an analgesic agent may offer significant advantages in the provision of pain relief when compared with intermittent i.m. injections. When used in conjunction with a PCA system, this method has the additional advantage of providing an objective comparison of the relative effectiveness of different analgesic drugs. The combination of an "active" PCA system and a "passive" background infusion regimen is particularly effective in treating pain (Welchew, 1983). In the present study we have demonstrated that a continuous i.v. infusion of LAS 1.8 g over 6 h can provide pain relief similar to that provided by a continuous infusion of morphine 10 mg over 6 h. Although the mean pain scores did not differ significantly throughout the trial period, the earlier pain scores of the patients in the morphine group were slightly lower than those of the patients in the LAS group (but it should be noted that the initial pain scores—obtained before injection of the trial drug in the recovery area—were higher in those patients subsequently receiving LAS). However, the fact that morphine had effected a slight reduction in pain score 30 and 60 min after the initial i.v. bolus, whereas LAS had not, does tend to suggest that LAS is either not quite as effective as morphine in relieving the severe pain immediately following pulmonary surgery, or that its onset of action is slower.

All patients were satisfied with the overall quality of pain relief (there being a slightly lower overall mean pain score in the LAS group), although when questioned after the infusion had been in progress for 3 h, 60% of patients (in both treatment groups) were experiencing moderate or severe pain. Stapleton, Austin and Mather (1979) also reported that more than 60% of patients who had undergone lower abdominal, as opposed to pulmonary surgery, experienced moderate or severe pain during the first 4 h of an infusion of pethidine. This was despite apparently effective blood concentrations which were 50–100% in excess of the suggested therapeutic concentration. These observations suggest that pain experienced early after operation is relatively refractory to effective treatment by drugs (narcotic or otherwise), but that a patient's memory for this early pain is poor.

Patient acceptance of the technique was high, with only one patient (in the LAS group) experiencing difficulty in the use of the PCA system. It was especially useful in allowing the full and vigorous physiotherapy which these patients require. The incidence of nausea and vomiting, and the need for anti-emetic drugs, were almost identical in the two groups. This is in contrast to the findings of a previous study in which an infusion of LAS was associated with a lower incidence of these side effects (Cashman et al., 1984). It would seem that even the small dose of narcotic administered via the PCA system was responsible for a marked increase in these particular side effects. The incidence of drowsiness was greater in the morphine group, and whereas this may be an advantage following other types of major surgery, it is not necessarily so following pulmonary surgery. However, no patient in either group was noted to have a respiratory rate of less than 12 b.p.m.

For the purposes of the present study it was decided to utilize a verbal pain scoring system. This was first described by Keele in 1948. We believe that the advantages of this system outweigh the disadvantages. Not only does it benefit from being simple and easily understood, but it was anticipated that there might be problems with the use of a visual analogue scale in the period early after operation, when the patients were still under the influence of general anaesthesia. Furthermore, because of the nature of the surgery being performed, patients were expected to experience difficulty in using their dominant arm to mark a visual analogue scale, regardless of the side on which surgery had been performed.

Aspirin is known to influence platelet function and an adverse effect on haemostasis would limit its clinical usefulness as a parenteral analgesic. We have demonstrated that patients receiving an infusion of LAS 7.2 g over 24 h (equivalent to acetyl salicylic acid 4.0 g) do not have a greater blood loss after operation than patients receiving morphine. Acetyl salicylic acid is now known to have a paradoxical effect on the bleeding time as a result of a dose-dependent differential action on the platelet aggegating inhibitor, prostacyclin, and the pro-aggregating thromboxane (O'Grady and Moncada, 1978). Acute doses of less than 1 g have been shown to prolong bleeding time, whilst larger doses are associated with no prolongation of bleeding time (Rajah, Penny and Kester, 1978).

We feel that the present study has also demonstrated a novel and effective approach to the relief of pain after operation, namely the use of a continuous infusion of a non-narcotic analgesic coupled with a PCA system administering small incremental doses of a narcotic analgesic. However, it should be emphasized that, as a result of the double-blind randomized nature of the trial, the maximum dose of on-demand analgesia was identical for both treatment groups. Despite the sub-optimal increments that this caused the patients in the LAS group to receive, the pain scores were not appreciably greater in the early period after operation, and were actually lower in the later period. In practice, it is to be anticipated that larger incremental doses or a shorter lock-out time could be used, with obvious advantages for the quality of the analgesia obtained.

In conclusion, an infusion of LAS 1.8g 6-hourly following major thoracic surgery has been shown to provide a quality of pain relief similar to that derived from an infusion of morphine 10mg 6-hourly. The combination of an infusion of a non-narcotic coupled with a Patient Controlled Analgesic system administering small increments of a narcotic analgesic has proved to be a safe and effective method of providing pain relief after major surgery.

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CONTINUOUS EXTRADURAL INFUSION OF 0.0625% OR 0.125% BUPIVACAINE FOR PAIN RELIEF IN PRIMIGRAVID LABOUR

D. F. LI, G. A. D. REES AND M. ROSEN

SUMMARY

The efficacy of an extradural infusion of 0.0625% or 0.125% bupivacaine was studied in 98 primigravid mothers in active labour. No special measures were taken to posture the mother (except to avoid aorto–caval compression). The study regimen included a control group (no infusion) receiving intermittent top-ups (0.25%. bupivacaine 8–10 ml), two groups receiving bupivacaine 6.25 mg h^{-1} infusion in different concentrations (0.0625% and 0.125%), a fourth group receiving 0.125% bupivacaine 12.5 mg h^{-1} infusion, and a fifth group receiving 0.125% bupivacaine 18.75 mg h^{-1} infusion. The optimum infusion rate was 0.125% bupivacaine 10 ml h^{-1}, at which 69% of primigravid mothers required none or only one "top-up" of 0.25% bupivacaine 8–10 ml during a mean duration of 7.1 h labour. In the group who had no extradural infusion, only 32% of mothers managed with one or no top-up. The median interval between top-ups was increased from 145 min in the no infusion group to 245 min in those mothers receiving 0.125% bupivacaine 10 ml h^{-1} by infusion. Increasing the rate of infusion to 15 ml h^{-1} did not improve the results. Spread of local anaesthetic to higher levels was limited (<T5) so that testing sensory loss at the T5–6 level at 2-hourly intervals should detect accidental spinal blockade resulting from inadvertent intrathecal infusion.

Continuous extradural analgesia is practised widely to relieve pain in labour. However, intermittent "top-ups" of local anaesthetic agents cause "surges" of calls upon medical and midwifery staff and, occasionally, marked changes in maternal cardiovascular function. Previous studies have shown the effectiveness of a continuous infusion with either 0.25% or 0.375% bupivacaine although frequent manipulation of the patient's posture was required to optimize pain relief (Glover, 1977; Evans and Carrie, 1979; Matouskova, Hanson and Elmen, 1979; Davies and Fettes, 1981; Taylor, 1983). This approach appears to offer better haemodynamic stability, and should avoid delay in topping-up when anaesthetic or midwifery staff are busy. However, the potential risk of a dural puncture by the catheter during infusion remains a cause for concern. Hence, a compromise between efficacy and safety has been sought by using a "safe" volume of a solution of lower concentration. It has been shown by Kenepp, Cheek and Jutsche (1983) that, with the same total dose of infused bupivacaine, a 0.125% solution blocks more dermatomes than does either a 0.25% or 0.5% solution, possibly because a larger volume of fluid was infused. Clinical experience with the 0.125% concentration is inadequate as previous reports involved either a small number of patients or a short duration of infusion (less than 2 h) (Glover, 1977; Clark, 1982). The present study was designed to assess the use of low concentrations of bupivacaine for extradural infusion in a controlled manner, and to determine the optimal volume of infusion necessary to prolong effectively the interval between top-ups in patients in active labour.

PATIENTS AND METHODS

Primigravid mothers in active labour who requested extradural analgesia were included. The plan of investigation was approved by the ethics committee, and consent obtained from each patient. All mothers

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received Hartmann's solution 500–1000 ml before the local anaesthetic was injected. Lumbar extradural blockade was performed via the L2–3 or L3–4 intervertebral space with a 16-gauge Tuohy needle. A catheter (Portex) was inserted leaving about 3–4 cm inside the extradural space. Ten millilitre of 0.5% bupivacaine was given initially and the effects assessed after 10–15 min. Solutions of 0.125% and 0.0625% bupivacaine were prepared by dilution of 0.5% bupivacaine 62.5 ml in physiological saline 187.5 ml and 0.5% bupivacaine 31.25 ml in physiological saline 218.75 ml, respectively. The patients were then randomly allocated to the following groups:

Group I: control group with no infusion.
Group II: 0.0625% bupivacaine infusion at 10 ml h^{-1} (6.25 mg h^{-1})
Group III: 0.125% bupivacaine infusion at 5 ml h^{-1} (6.25 mg h^{-1})
Group IV: 0.125% bupivacaine infusion at 10 ml h^{-1} (12.5 mg h^{-1})

An additional group (group V) was added to determine whether a more rapid flow improved results:
Group V: 0.125% bupivacaine infusion at 15 ml h^{-1} (18.75 mg h^{-1})

The infusion was given by an IMED volumetric pump through a bacterial filter. At first, mothers were assessed every 60 min for the extent of sensory and motor blockade, but it became obvious that this was unnecessary, and assessment was carried out every 2 h. The sensory level was determined by pinprick and lower limb weakness graded on a scale from 0 to 3 (Bromage, 1978). Arterial pressure was measured every 30 min and at 5-min intervals for 30 min following each top-up. The fetal heart was monitored continuously. If analgesia was considered inadequate by the mother, a top-up was given (0.25% bupivacaine 8–10 ml) and the time recorded. No special attempt was made to position the mother except to avoid aorto–caval compression.

At delivery, a top-up was administered if perineal analgesia was inadequate. The mode of delivery, duration of labour and condition of the baby were recorded. Venous blood samples were taken from the mother and from the umbilical cord for analysis of bupivacaine concentration. The samples were stored at −20 °C until analysed. Each mother was interviewed the day after delivery. The overall assessment of pain relief, degree of drowsiness and sickness experienced in labour were determined by 10-cm linear analogue scales. The durations of sensory and motor loss after delivery were noted. The condition of the baby was assessed by the mother and by the observer.

The results were analysed by *t* test, chi-square test with Yates' correction and one-way variance analysis. The intervals between top-ups were analysed by the log-rank test (see below).

TABLE I. *Patient data (mean (SD)). There were no statistical differences between the five groups.*

	Group I	Group II	Group III	Group IV	Group V
Bupivacaine Concentration	—	0.0625%	0.125%	0.125%	0.125%
Infusion dose (mg h^{-1})	0	6.25	6.25	12.5	18.75
No. of patients	19	20	20	19	20
Age (yr)	24.1 (4.1)	24.1 (4.4)	23.8 (4.7)	24.8 (5.0)	25.5 (6.2)
Height (cm)	158.8 (5.1)	160.6 (6.4)	160.1 (4.9)	158.8 (6.1)	161.9 (7.5)
Length of gestation (weeks)	40.5 (1.4)	40.0 (1.6)	40.5 (1.2)	39.8 (1.2)	40.5 (1.1)
Duration of labour (h)					
1st stage	11.5 (4.9)	11.3 (3.6)	11.0 (4.8)	10.5 (5.3)	12.9 (5.1)
2nd stage	2.0 (1.1)	1.7 (0.9)	1.9 (1.3)	1.8 (1.0)	1.7 (1.0)
Birth weight (kg)	3.4 (0.4)	3.3 (0.4)	3.3 (0.4)	3.3 (0.6)	3.4 (0.5)

RESULTS

Ninety-eight primigravid mothers were included. Mothers with extradural blockade–delivery intervals of less than 3 h were excluded from the statistical analysis. There were no significant differences between any group of patients (including group V) in age, height, gestational period or birth weight (table I). The duration of the first stage of labour varied between a mean of 10.5 h and 12.9 h, and the mean durations of the second stage from 1.7 to 2.0 h (ns).

The mean interval between the induction of the extradural blockade and delivery ranged from 7.1 h to 8.6 h (ns), and the mean total dose used from 135.2 mg to 197.9 mg ($P < 0.05$) (table II). In only three patients did the total dose required exceed 300 mg: a mother in group II received 330 mg over 12 h; another in group III received 337 mg over 15 h; and a third in group V required 350 mg over 14 h. The mean dose per hour for each group showed a progressive increase in the amount of bupivacaine with increasing infusion dose ($P < 0.005$) (table II). There were, however, no significant differences between the results in groups II and III, that is mothers who received the same total dose given in different concentrations.

Fifty-two per cent of primigravid mothers required three or more top-ups when no infusion was given, compared with 5% and 0% who had 0.125% bupivacaine 10 or 15 ml h^{-1} (table III). Sixty-nine percent of mothers required none or only one top-up with an infusion of 0.125% bupivacaine 10 ml h^{-1}. This compares favourably with 32% in the control group and 35% and 45% of the mothers receiving 6.25 mg h^{-1} infusion (groups II and III, respectively). When the infusion rate was increased to 0.125% bupivacaine 15 ml h^{-1}, the number who required one or less top-up increased to 70%. Only one mother who received an infusion at 12.5 mg h^{-1} required more than two top-ups.

The time of each top-up was recorded and each interval representing the duration of adequate analgesia calculated. For most mothers in the period from the final dose to delivery, adequate analgesia was maintained right up to the time of delivery (and could have extended beyond this time). Some mothers had a top-up immediately before operative delivery. In those patients the last duration was discarded.

Cumulative percentage graphs were drawn for the durations of adequate analgesia for each infusion regimen (fig. 1). This included all periods for each group, that is, several per subject. Groups were compared by the log-rank test (Peto et al., 1976, 1977) which was also used to examine variations between subjects within groups. In the control group the interval between top-ups varied between 25 min and 270 min with a median interval of 145 min. In the group receiving 0.0625% bupivacaine 10 ml h^{-1}, intervals varied between 90 min and 430 min (median duration of 190 min). In the group receiving 0.125% bupivacaine 5 ml h^{-1}, the interval between top-ups varied between 40 min and 462 min with a median interval of 195 min; these are similar means.

At an infusion rate of 0.125% bupivacaine

TABLE II. *Duration of extradural infusion and total dose of bupivacaine (mean (SD)). †No statistical differences between the five groups;* *$P<0.05$ *(between each group);* **$P<0.005$ *(between each group)*

	Group I	Group II	Group III	Group IV	Group V
Bupivacaine Concentration	—	0.0625%	0.125%	0.125%	0.125%
Infusion dose (mg h^{-1})	0	6.25	6.25	12.5	18.75
Extradural – delivery interval (h)†	7.7 (3.1)	8.6 (2.6)	8.4 (3.0)	7.1 (2.3)	8.1 (2.6)
Total dose used in labour (mg) (loading + infusion + 1st stage top-ups)*	135.2 (52.2)	165.2 (67.2)	170.8 (64.9)	161.0 (52.0)	197.9 (63.6)
Mean dose per hour (mg h^{-1})**	18.9 (6.4)	19.2 (5.0)	20.9 (4.8)	23.6 (7.9)	24.7 (3.0)

TABLE III. *Percentage of patients requiring top-ups in labour.* $P<0.005$*: no significant differences between groups II and III, and IV and V*

	Group I	Group II	Group III	Group IV	Group V
Bupivacaine Concentration	—	0.0625%	0.125%	0.125%	0.125%
Infusion dose ($\mathrm{mg\,h^{-1}}$)	0	6.25	6.25	12.5	18.75
No. top-ups					
0	0	10	5	21	35
1	32	25	40	48	35
2	16	35	25	26	30
3+	52	30	30	5	0

10 ml h^{-1}, the intervals varied between 38 min and 438 min with a median interval of 245 min. Variations between the first four groups were highly significant (chi-square = 22.65, d.f. = 3, $P < 0.001$). Variation between subjects was no greater than would be expected had each duration come from a different individual (chi-square = 71.02, d.f. = 74, ns). When the infusion rate of 0.125% bupivacaine was set at 15 ml h^{-1}, the median interval of 265 min was not significantly different from that noted in those mothers receiving 0.125% bupivacaine 10 ml h^{-1}.

Only one mother had a sensory block which extended up to T4 during infusion (table IV). The degree of lower limb paralysis did not vary greatly between groups. The mode of delivery was not related to the infusion regimen.

The overall pain, drowsiness and nausea scores at the postnatal interview (table V) showed no important differences. Babies were active and alert when examined on the second day. Only eight had any complication during delivery—all unrelated to extradural analgesia.

Excluding those from mothers who had the last

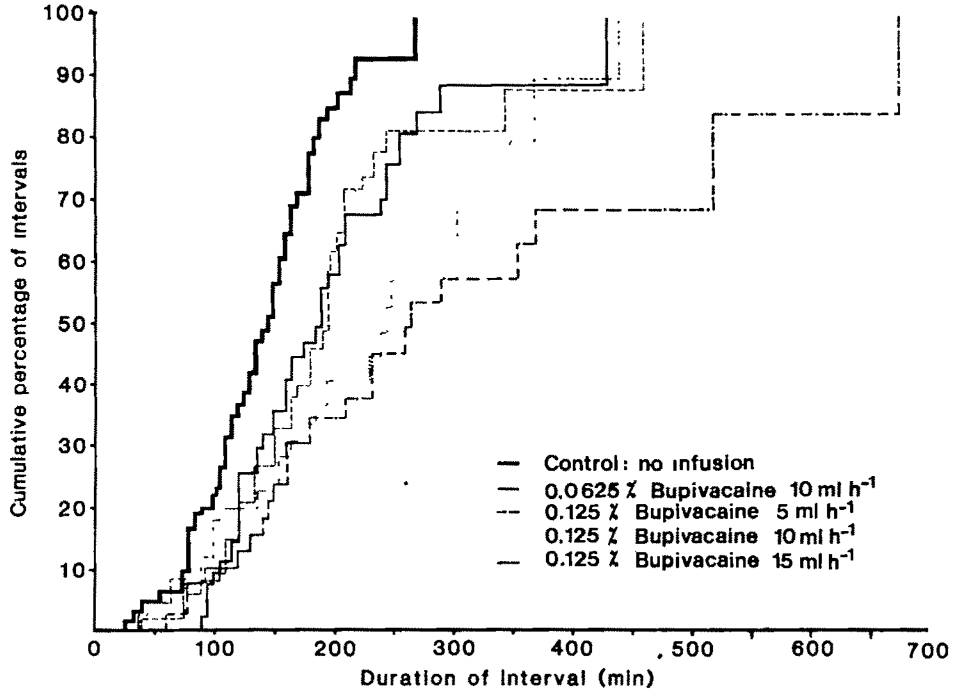

FIG 1. Cumulative percentage of intervals between top-ups for each bupivacaine infusion regimen.

TABLE IV. *Degree of sensory and motor blockade. Grade 0 = flexion of hip, knee and ankle; grade I = flexion of knee and ankle only; grade II = flexion of ankle only, grade III = unable to move leg or foot. *No statistical differences between the five groups*

	Group I	Group II	Group III	Group IV	Group V
Bupivacaine					
Concentration	—	0.0625%	0.125%	0.125%	0.125%
Infusion dose ($mg\,h^{-1}$)	0	6.25	6.25	12.50	18.75
Highest level of analgesia	T6	T8	T6	T4	T5
Degree of motor block*					
Grade 0	5.3%	5%	5%	0%	0%
Grade I	10.5%	25%	10%	21%	30%
Grade II	47.4%	50%	50%	73 7%	55%
Grade III	36.8%	20%	35%	5.3%	15%

top-up given for operative delivery (forceps and Caesarean section), 44 paired blood samples were available for bupivacaine analysis (table VI). At delivery, venous bupivacaine concentrations were greater in those mothers who had an extradural infusion than in control subjects, and ranged from 0.325 $\mu g\ ml^{-1}$ to 0.543 $\mu g\ ml^{-1}$. This difference was not statistically significant ($P = 0.175$). The bupivacaine concentration in the umbilical cord remained low both in controls and in mothers receiving the extradural infusion ($P = 0.38$).

DISCUSSION

In this study mothers with an extradural blockade–delivery interval of less than 3 h were excluded. This decision was taken since the initial loading dose could be effective within this period and would bias the results from the infusion; this was confirmed by the findings in the control group: 50% of mothers had adequate analgesia for over 2 h after a single extradural dose of bupivacaine. Therefore, previous studies in which an infusion was given for less than 2 h may not be valid (Evans and Carrie, 1979; Clark, 1982).

No special manipulation of the mother's posture was attempted. The physical behaviour of the infusion of bupivacaine in the extradural space is still far from clear (Bromage, 1978). Frequent manipulation of labouring mothers causes excessive stress on the midwifery staff and inconvenience to the mothers. Time spent on frequent postural changes allowing infusions to "catch-up" could then be greater than giving top-ups in the usual way.

A continuous infusion of 0.125% bupivacaine 10 ml h^{-1} resulted in 69% of these primigravid mothers requiring no or only one top-up. This is in agreement with the findings of Matouskova, Hanson and Elmen (1979) with 0.25% bupivacaine

TABLE V. *Results of postnatal interview (mean (SD)). There were no statistical differences between the five groups for each of the three scores*

	Group I	Group II	Group III	Group IV	Group V
Bupivacaine					
Concentration	—	0.0625%	0.125%	0.125%	0.125%
Infusion dose ($mg\,h^{-1}$)	0	6.25	6.25	12.50	18.75
Pain score	30.2 (23.2)	34.5 (25.2)	41.0 (26.4)	45.3 (28 2)	41.9 (18.0)
Drowsiness score	32.8 (28.6)	24.2 (28.6)	30.9 (36.0)	25 8 (29.0)	31.3 (28.5)
Nausea score	22 6 (27.5)	20.4 (23.9)	9.2 (17.5)	17.0 (21.9)	24.1 (29.6)

TABLE VI *Maternal and cord blood concentrations of bupivacaine (mean (SD))* * P <0.02; ** P $= 0.175$; † P $= 0.38$; ‡P $= 0.06$

	Group I	Group II	Group III	Group IV	Group V
Bupivacaine Concentration	—	0.0625%	0.125%	0.125%	0.125%
Infusion dose (mg h^{-1})	0	6.25	6.25	12.5	18.75
No. of paired samples	10	9	6	11	8
Last bolus dose–delivery interval* (h)	1.68 (1.36)	1.87 (1.11)	3.70 (2.63)	3.31 (1.52)	3.75 (1.50)
Maternal concn MV** (ug ml^{-1})	0.240 (0.088)	0.328 (0.095)	0.543 (0.606)	0.438 (0.194)	0.325 (0.146)
Umbilical cord concn UV† (ug ml^{-1})	0.164 (0.083)	0.152 (0.118)	0.122 (0.034)	0.159 (0.051)	0.103 (0.038)
UV/MV‡	0.67 (0.28)	0.44 (0.26)	0.45 (0.31)	0.41 (0.16)	0.37 (0.17)

infused at 5 ml h^{-1}. When the infusion rate was increased by 50% to 15 ml h^{-1}, the percentage of success did not increase. This plateau of effect was also evident in the median intervals between top-ups.

In each test group the median duration between top-ups was 145, 190, 195, 245 and 265 min, respectively. A regression of the median interval between top-ups follows a straight line with increasing dose of infusion until a plateau is reached at the higher doses (fig. 2). Therefore 0.125% bupivacaine 10 ml h^{-1} appears optimal.

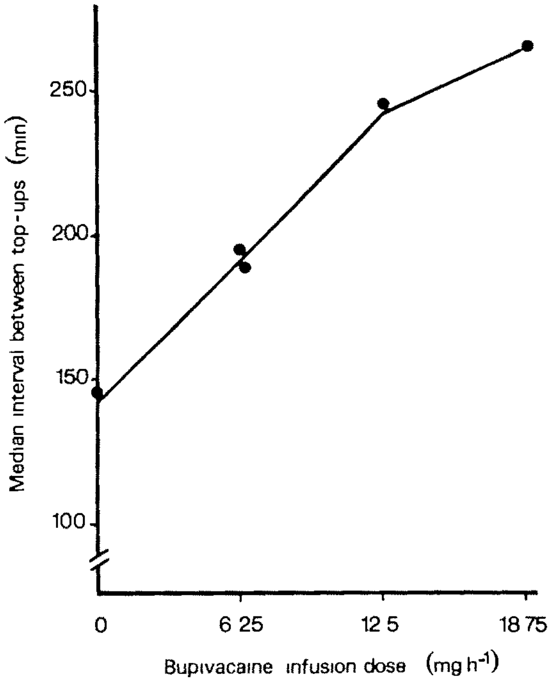

FIG 2. Regression of the median intervals between top-ups for each bupivacaine infusion dose.

Considering results from mothers having the same dose but at different concentrations and volumes (group II and group III), the cumulative percentages (fig. 1) of the two groups were very close and median durations of analgesia were 190 and 195 min, respectively. This indicates that more fluid in the extradural space did not provide longer analgesia and that the total dose of local anaesthetic was the decisive factor. This is in disagreement with the findings of Kenepp, Cheek and Gutsche (1983) that low concentrations of bupivacaine are more effective than higher concentrations in extradural infusion. This finding is in fact in agreement with Bromage's findings with the use of intermittent top-ups for continuous extradural analgesia (Bromage, 1978).

The safety of continuous extradural infusion with local anaesthetics remains a matter of concern to anaesthetists. Inadvertent puncture of the dura during infusion has been recorded (Matouskova, Hanson and Elmen, 1979). However, results from studies on bupivacaine used for subarachnoid analgesia give some indication of possible effects. After a bolus injection of 0.5% bupivacaine 15–20 mg, blockade usually does not extend above T4 (Chambers, Edstrom and Scott, 1981; Kalso, Tuominen and Rosenberg, 1982; Tuominen, Kalso and Rosenberg, 1982; Russell, 1983; Ryan, Pridie and Copeland, 1983; Sheskey et al., 1983; Tattersall, 1983). The block then regresses at about two segments per hour. Therefore, by infusing a dose of bupivacaine 12.5 mg h^{-1} steadily, it is unlikely that total spinal blockade with respiratory paralysis would occur quickly (or even at all) if dural puncture occurred. There should be at least 2 h of warning before the blockade extended higher than T9–10 during obstetric analgesia. Sensory testing at T5–6 at 2-hourly intervals would detect advancing spinal blockade arising from inadvertent intrathecal infusion. In our series, admittedly small, only one patient had a block reaching T4, so that with this regimen there would have been only one false alarm with the proposed procedure. Therefore, it is advocated that testing the level at T5–6 (marked clearly) every 2 h during an infusion should be easily accepted by midwives.

The bupivacaine concentrations in both mother and baby at delivery were well within the safety range of 1.5–2.3 µg ml^{-1} (Widman, 1966; Jorfeldt, et al., 1968; Hollmen, Kerhonen and Ojala, 1969; Reynolds and Taylor, 1971). The higher maternal bupivacaine concentraton in the groups receiving an infusion probably related to the higher total dose used in these mothers. However, the umbilical cord bupivacaine concentration remained constantly low. This may be related to the higher protein-binding capacity of bupivacaine and the steady input of a small bupivacaine dose to the mother during infusion, compared with the high fluctuating concentration of intermittent top-ups. The results obtained agree with previous reports that the continuous extradural infusion of bupivacaine is safe for both mother and fetus (Glover, 1977; Evans and Carrie, 1979; Matouskova and Hanson, 1979; Clark, 1982).

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BUPRENORPHINE-SUPPLEMENTED ANAESTHESIA

Influence of Dose on Duration of Analgesia after Cholecystectomy

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SUMMARY

Fifty-one patients undergoing cholecystectomy received a single dose of buprenorphine 4.5–12 $\mu g\ kg^{-1}$ at induction. Median duration of analgesia after surgery was 6 h. Multiple regression analysis showed the duration of analgesia to be slightly dependent on the age of the patient. No relationship was found between the duration of analgesia and the weight-related dose of buprenorphine, the age, sex or body weight of the patient, the duration of anaesthesia, or the dose of droperidol or thiopentone administered.

Buprenorphine is a narcotic analgesic with an agonist-antagonist action and an analgesic potency about 30 times that of morphine (Tigerstedt and Tammisto, 1980). Kamel and Geddes (1978) found a duration of action four to five times that of pethidine when buprenorphine was given as an analgesic after surgery.

Studies of the use of buprenorphine during surgery are few, and reports of the duration of analgesia following surgery have been equivocal. For example, Kay (1980) found a mean duration of analgesia of 12 h after laparotomy, whereas Hansen and colleagues (1981) noted that analgesia lasted for a median of 5 h after major surgery (predominantly cholecystectomy).

The present study was undertaken to ascertain whether the duration of analgesia following surgery was dependent on the dose of buprenorphine administered during the operation, or was influenced by other factors.

PATIENTS AND METHODS

Fifty-one consecutive healthy patients undergoing cholecystectomy were investigated. A regional ethics committee was not established at the time of the investigation, but informed consent was obtained from all patients.

On the morning of surgery, patients were premedicated with diazepam by mouth 5–20 mg depending on age, weight and physical status. Each patient received one single dose of buprenorphine at the induction of anaesthesia. The dose was drawn randomly by the attending anaesthesia nurse and varied between 4.5 and 12.0 $\mu g\ kg^{-1}$, with increments of 0.15 $\mu g\ kg^{-1}$. Neither the investigators nor the recovery ward staff were aware of the dose given. Anaesthesia was induced with droperidol 0.25 $mg\ kg^{-1}$, and a dose of thiopentone sufficient to abolish the eyelash reflex. Pancuronium 0.1 $mg\ kg^{-1}$ was given to facilitate orotracheal intubation. Anaesthesia was maintained with 67% nitrous oxide in oxygen. Supplementary doses of pancuronium, thiopentone or droperidol were given if indicated. After completion of surgery, neuromuscular blockade was antagonized with atropine 0.5–1.5 mg and neostigmine 1.0–2.5 mg, and the patients transferred to the recovery ward where they were observed until the following morning. During the recovery period, analgesics were given when requested by the patient.

The age, sex and weight of all patients were recorded. The duration of anaesthesia was recorded, as were the nature and doses of any other drugs given. The duration of analgesia was the interval in hours between the induction of anaesthesia and the administration of the first dose of analgesic after surgery.

Statistical analysis

The hypothesis that the duration of analgesia after

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surgery depends on the weight-related dose of buprenorphine was tested by multiple regression, linear as well as non-linear, analyses (Wonnacott and Wonnacott, 1977).

The basic linear regression model has the following form:

$$Y = a + b_1X_1 + b_2X_2 \ldots + b_iX_i \ldots + b_nX_n.$$

Y is the dependent variable and X_i are the independent variables. The constant a and the coefficients $b_1, b_2, \ldots b_i, \ldots b_n$ were calculated. The Statistical Package for the Social Sciences (SPSS) (Nie et al., 1975) was used for the statistical analysis (release 9.0–UW 1.0, July 1982) of the data on a digital computer (UNIVAC 1162, Sperry Univac). The interpretation of b_i is that if the X_i variable is changed by one unit, then Y changes b_i units. In this analysis Y is the duration of analgesia and the X_i are factors that may partly determine Y, for example, weight-related dose of buprenorphine, age, sex, weight, duration of anaesthesia, total dose of thiopentone and total dose of droperidol. This means that if X_1 is the weight-related dose of buprenorphine, then b_1 shows the change in duration of analgesia in units of 1-h periods if the dose is increased by 1 μg kg^{-1}.

The fit of the model is given by the determination coefficient, R^2, and a simultaneous F test. R^2 can be interpreted as the fraction of the total variation that is explained by the regression model. The F test is a test of the null-hypothesis: that all the coefficients b_i are equal to zero. Student's t test is a test of the null hypothesis: that each particular b_i is different from zero. This implies that only variables with particular b_i-coefficient significantly different from zero are entered in the model. Stepwise regression was used, and the 5% level of significance chosen.

For the variables that entered the model the tables show the b_i coefficient, the t value, and the P value.

RESULTS

Two patients were excluded from the analysis because of departure from the plan of investigation: results are presented from 49 patients.

Figure 1 shows the weight-related doses of buprenorphine and the corresponding values for the duration of analgesia, the latter having a median value of 6 h and a range of 2–24 h. Table I shows the X-variables studied, and tables II and III the results using the two statistical models. The variables not listed in tables II and III did not enter the model because their particular b_i coefficients were not significantly different from zero at the 5% level.

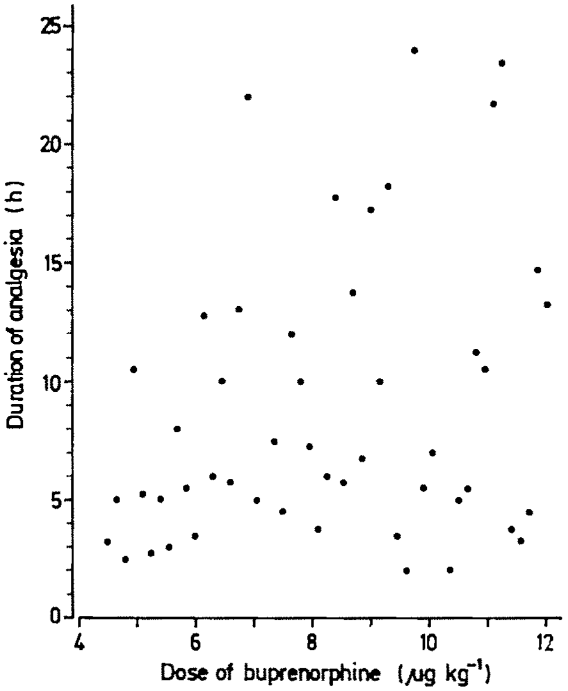

FIG 1. Relationship between duration of analgesia and dose of buprenorphine for the 49 patients included in the analysis

TABLE I *The variables (X) tested by multiple regression. Median values (range)*

Age (yr)	59 (22–82)
Sex	37F : 12M
Weight (kg)	70 (38–100)
Dose of buprenorphine (μg kg^{-1})	8.25 (4.5–12.0)
Dose of droperidol (mg)	17.5 (10–35)
Dose of thiopentone (mg)	350 (50–850)
Duration of anaesthesia (h)	2.25 (1.25–4.25)

TABLE II. *Results using a linear model. Duration of analgesia* = a + b_1 × *dose of buprenorphine* (μg *kg*$^{-1}$) + b_2 × *age* + b_3 × *weight* + b_4 × *duration of anaesthesia* + b_5 × *total dose of thiopentone* + b_6 × *total dose of droperidol* + b_7 × D. D = *0 if the patient is a male, and* D = *1 if the patient is a female. Fit of the model:* $R^2 = 0.09$; F *(1, 47) = 4.70;* P = *0.035. The table shows variables of which the coefficients were different from zero*

Variable	Coefficients	t	P
Age	b_2=0.125 a=1.68	2.18	0.035

TABLE III. *Results using a non-linear model. ln (duration of analgesia) = ln* a + b_1 × *ln (dose of buprenorphine* ($\mu g\ kg^{-1}$)) + b_2 × *ln (age)* + b_3 × *ln (weight)* + b_4 × *ln (duration of anaesthesia)* + b_5 × *ln (total dose of thiopentone)* + b_6 × *ln (total dose of droperidol)* + b_7 × D. D = *0 if the patient is a male, and* D = *1 if the patient is a female. Fit of the model:* $R^2 = 0.082$; F *(1, 47)* = *4.18;* P = *0.047. The table shows variables of which the coefficients were different from zero*

Variable	Coefficients	*t*	*P*
Age	$b_2=0.63$ $\ln a=-0.58$	2.044	0.047

DISCUSSION

This study has shown that, in the dose range 4.5–12.0 $\mu g\ kg^{-1}$, the duration of analgesia after buprenorphine-supplemented anaesthesia did not depend on the weight-related dose of buprenorphine, nor did it depend on the duration of anaesthesia, the weight or sex of the patient, or the dose of thiopentone or droperidol administered. The only variable that had a significant correlation with the duration of analgesia was the age of the patient; the older the patient, the longer the duration of analgesia. However, age accounted for only 9% of the variation in the duration of analgesia. The remaining 91% of the variation could not be accounted for by the variables studied. Another important finding was the relatively short duration of analgesia (median value 6 h) when compared with the reports of Kamel and Geddes (1978) and Kay (1980).

Other studies on the duration of analgesia after buprenorphine-supplemented anaesthesia have compared a fixed dose of buprenorphine with another analgesic (Kay, 1980) or compared three fixed doses of buprenorphine with another analgesic (Abrahamsson et al., 1982). The design of the present study was quite different, as 51 different doses were given. Analysing the data by multiple regression made it possible to define which of the variables studied influenced the duration of analgesia, and to calculate the degree of influence of each. As the site of operation could also affect the duration of analgesia (Bellville et al., 1971), this variable was kept constant.

Hovell (1977) found that buprenorphine 4 and 8 $\mu g\ kg^{-1}$ given after surgery was superior to 2 $\mu g\ kg^{-1}$ in regard to difference in pain intensity, although there was no apparent difference between 4 and 8 $\mu g\ kg^{-1}$. Abrahamsson and colleagues (1982) compared buprenorphine 5, 10 and 15 $\mu g\ kg^{-1}$ with fentanyl given during surgery. Postoperative analgesia lasted longer after buprenorphine, but there was no difference in duration between the three buprenorphine groups. The findings in these two studies are in agreement with the present study; this is in contrast to Watson and co-workers (1982), who found a longer duration of analgesia with buprenorphine 0.6 mg than 0.3 mg, given i.v. after surgery. However, the patients in that study underwent total hip replacement, and the disparity between theirs and the present results may be explained by the difference in surgical procedure.

Bellville and colleagues (1971) investigated the relationship between certain patient characteristics and pain relief with morphine or pentazocine after surgery. Age correlated highly with relief of pain, the older age groups reporting more relief. No other patient characteristic seemed to influence the relief of pain, including weight-related dose of the analgesic.

In the present study it has been shown that 91% of the variation in the duration of analgesia was not accounted for by the variables that were assessed. It is possible that some of the variables influencing the duration of analgesia should be sought in psychological, rather than physiological, factors (Boyle and Parbrook, 1977; Austin, Stapleton and Mather, 1980).

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Br. J. Anaesth. (1985), 57, 275–284

FENTANYL AND BUPIVACAINE MIXTURES FOR EXTRADURAL BLOCKADE

F. S. RUCCI, M. CARDAMONE AND P. MIGLIORI

SUMMARY

In a prospective double-blind study, single dose lumbar extradural blockade was instituted in 80 healthy male patients undergoing lower abdominal surgery. Patients were assigned randomly to one of four groups. Each group received treatment with 0.5% bupivacaine 20 ml containing adrenaline 1:200 000. To this solution was added fentanyl 0, 50, 100 or 200 µg. The time to regression of analgesic blockade was significantly prolonged (P < 0.05) only with mixtures containing fentanyl 200 µg; no effect was demonstrated with lower doses of the opioid. However, the degree of motor blockade was less intense and incomplete S1-blockade (root-jumping) was more frequent with mixtures containing increasing doses of fentanyl. Patients treated with bupivacaine–fentanyl mixtures shivered less than the control group and showed fewer instances of acute hypotension The side-effects observed were minor.

In clinical practice the ideal local anaesthetic should combine rapid onset and a long duration of action (Cunningham and Kaplan, 1974). At present, no anaesthetic agent has such characteristics, but there have been numerous studies of the effects of mixtures of different anaesthetic solutions in an attempt to combine the two properties (Defalque and Stoelting, 1966; Brodsky and Brock-Utne, 1978; Galindo and Witcher, 1979; Cohen and Thurlow, 1979; Kankinen, Kankinen and Eerola, 1980; Seow et al., 1982; Magee, Sweet and Holland, 1983).

There have been no investigations on the effects of mixtures of an anaesthetic solution and an opioid drug, in spite of the increasing practice of giving spinal opioids, and it remains to be established whether such a combination is able to reduce the latency of an extradural block and prolong its effectiveness. Mixtures of this type are used increasingly in an empirical way, but knowledge of their application is still limited. The effects of the association of an opioid with a local anaesthetic in extradural (De Castro et al., 1980; Shapiro et al., 1981; Justin et al., 1982) and in subarachnoid blockade (Cunningham, McKenna and Skene, 1983; Kalso, 1983; Takasaki and Asano, 1983) have been investigated little, or without control studies. Since interest has been focused almost entirely on the analgesic effect during the period immediately after operation, rather than on the characteristics of the sensory and motor blockade, mixtures of a local anaesthetic and morphine have been preferred (Shapiro et al., 1981; Muller et al., 1981; Cunningham, McKenna and Skene, 1983; Kalso, 1983; Takasaki and Asano, 1983).

The aim of this study was to compare, under controlled conditions, the effectiveness and the side effects of mixtures of bupivacaine with increasing doses of fentanyl, on lumbar extradural blockade. We chose fentanyl as the opioid to be added to the anaesthetic solution because of its high lipid solubility (Von Cube et al., 1970). Unlike morphine, fentanyl easily crosses the lumbar dura (Moore et al., 1982) and penetrates quickly the lipid phase of underlying tissues of the cord. Thus, analgesia will be rapid (Devaux et al., 1982; Pierrot et al., 1982), intense (Stoyanov et al., 1981; Torda and Pybus 1982a, b; Welchew and Thornton, 1982) and sharply segmental (Bromage, 1982; Justin et al., 1982), with few side-effects from migration of the opioid in a rostral direction (Bromage et al., 1982a, b; Morgan, 1982).

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TABLE I. *Composition of local anaesthetic – fentanyl mixtures and characteristics of patients assigned to each group. *All solutions contained 1·200 000 adrenaline*

	Group B.F 0	Group B·F 50	Group B·F 100	Group B:F 200
0.5% Bupivacaine (ml)*	20	20	20	20
Fentanyl (μg)	0	50	100	200
Volume injected (ml)	20	21	22	24
Patient characteristics (mean (SD))				
Age (yr)	56 (16)	52 (13)	60 (12)	52 (14)
Weight (kg)	69 (7)	69 (10)	73 (8)	74 (8)
Height (cm)	167 (5)	167 (6)	169 (4)	169 (8)
Duration of op. (min) (mean (SD))	63 (31)	53 (28)	54 (28)	47 (25)
Herniorraphy (No. patients)	10	14	13	15
Prostatectomy (No. patients)	10	6	7	5

PATIENTS AND METHODS

Eighty male patients, ASA I or II, undergoing lower abdominal surgery (herniorraphy and prostatectomy), were studied. After detailed explanation of the study, informed written consent was obtained the day before surgery. The patients were allocated, on the basis of the date (but not year) of their birth, to four groups of 20 subjects each: group B:F 0 received 0.5% bupivacaine 20 ml without fentanyl; group B:F50 0.5% bupivacaine 20 ml with fentanyl; 50 μg; group B:F100 0.5% bupivacaine 20 ml with fentanyl 100 μg; group B:F 200 0.5% bupivacaine 20 ml with fentanyl 200 μg. All the solutions contained adrenaline 1:200 000. Details of the solutions and the patients are shown in table I.

No patient was pre-medicated. Before extradural blockade was begun, an i.v. cannula was inserted and an infusion of 500 ml of plasma expander (Emagel 30 drops min^{-1}) with metaraminol 160 μg was commenced. Atropine 0.5 mg i.v. was given. Arterial pressure (Riva–Rocci), heart rate and respiratory frequency were recorded before the blockade and every 5 min after extradural injection.

One anaesthetist performed the extradural blockades at L3–L4, with the patient lying on his side. The solutions to be injected were mixed at the bedside and were administered through a 16-swg Tuohy needle with the bevel upwards, at a speed of 1 ml s^{-1}. The patient was then turned supine and a separate assessor, who was unaware of the drug injected, commenced clinical observations of sensory and motor blockade.

Sensory blockade was assessed every 2 min for at least 30 min, or until the beginning of surgery. Blockade was identified by the loss of sensation of pin-prick from a 22-swg needle. Latency of onset was defined as the time between the extradural injection and the appearance of analgesia in any one dermatome (usually T12 and L1) bilaterally. The time of maximal diffusion was defined as the time necessary for the area of analgesia to reach its maximum spread. S1 latency was defined as the time at which blockade occurred bilaterally at that dermatome; it was determined from the disappearance of sensation of pain in the lateral region of the foot and in the little toe. If the analgesia was only unilateral, the S1 block was considered incomplete and the patient was assigned to the "root-jumping" group.

Duration of the block was recorded as follows:

(1) Regression of two segments (−2S): the time from complete spread to the bilateral regression of two dermatomes.

(2) Regression of four segments (−4S): the time from maximum spread to the bilateral regression of four dermatomes.

(3) Regression of last chest dermatome (−T12): the time between the onset of the block and the bilateral disappearance of analgesia from dermatome T12, which supplies the lower region of the abdomen.

Blocking time of S1 and the regression time of the last dermatome were each recorded from bilateral appearance of analgesia (onset) to offset.

Motor blockade in the lower limbs was assessed both subjectively and objectively. Subjective motor blockade was deemed to start when "numbness" appeared in the patient's legs, and to stop when the legs were again entirely "free". Objective motor blockade was evaluated every 5 min for at least 30 min, or until the beginning of surgery, with the "myotome scale" of Last (1978), according to which, particular movements of the legs are related to specific myotomes. Thus, hip flexion depends on L2 and L3; knee extension on L3 and L4; ankle dorsiflexion on L4 and L5 and plantar flexion on S1 and S2. These movements were given the scores: 0 = movement possible: complete lack of motor blockade; 1 = movement partially impeded: partial motor blockade; 2 = incapacity of movement: complete motor blockade. Taking into account the four movements for each limb, the lowest possible score was zero (absence of muscular block) and the highest, 16 (complete muscular block). This score was regarded as the most practical, albeit indirect, assessment of accompanying abdominal muscle relaxation.

The time to onset of partial motor blockade was defined as the time required for any one of these movements to be scored as 1, whereas the latency of complete motor blockade was the time elapsed to achieve a score of 2. The maximum intensity of the motor block was defined as the highest score reached, and the regression of objective motor blockade defined as the return of the myotome score to zero. After surgery, clinical evaluation of the sensory and motor profiles was continued in the recovery room at 15-min intervals until the complete return of sensory and motor functions.

Possible side effects were sought both during and after surgery. During surgery we recorded all the incidents of acute hypotension which required management with metaraminol 160 μg i.v., whether patients were awake or drowsy; and if they were affected by shivering, nausea or vomiting. Eight hours after surgery, the patients were questioned again, special care being paid to the appearance of headache, dizziness, nausea, vomiting, itching and retention of urine. No attempt was made to treat side effects, unless they were considered dangerous. In the case of prolonged retention of urine, naloxone 0.4 mg was injected slowly i.v.

During the first 3 days after surgery, intestinal transit was assessed by questioning about the first passing of flatus. Before the patient was discharged, we tested the acceptability of the anaesthetic techniques by asking the patient if he had found it satisfactory and if he would accept the same technique in case of another operation.

Parametric data were subjected to analysis of variance (ANOVA) and "*a posteriori*" comparisons were made using the Newman–Keuls test. For non-parametric data, diversity between groups was tested by the non-parametric analysis of variance (Kruskal–Wallis test) and by the chi-square test. Spearman non-parametric correlation and the test for linear trend in proportions were used to examine

TABLE II. *Bilateral sensory blockade (mean values (SD)). *Probability of significant difference among group (ANOVA, Test for linear test in proportions). †Significant difference ($P<0.05$) v. other groups (Newman–Keuls test). §Two patients were added, previously treated with B:F 0*

	Group B:F 0	Group B·F 50	Group B.F 100	Group B·F 200	*P**
Injection to onset (min)	11 (3)	11 (3)	10 (2)	12 (3)	ns
Injection to complete spread (min)	19 (3)	18 (4)	19 (5)	16 (5)	ns
Onset to complete spread (min)	8 (4)	7 (4)	9 (6)	4 (5)	<0.05
Number of segments involved	17.95 (2.37)	16.85 (2.64)	18 48 (3.03)	18.18 (2 57)	ns
Height of block (thoracic dermatome)	4.05	5 15	3.52	3 82	
S1 block onset (min)	29 (24)	21 (10)	18 (7)	24 (11)	ns
No patients with complete S1 blockade	16/20	12/20	15/22§	7/20	<0.05
S1 block duration (min)	154 (81)	180 (87)	161 (81)	219 (39)	ns
–2S regression (min)	128 (44)	129 (59)	130 (44)	183 (44)†	<0.01
–4S regression (min)	160 (45)	172 (64)	152 (48)	211 (38)†	<0.01
–T12 regression (min)	200 (52)	210 (61)	200 (55)	249 (40)†	<0.01
Last dermatome regression (min) (unless S1)	212 (47)	217 (65)	213 (62)	252 (41)	ns

variables as a function of the concentrations of opioid. When the phenomena studied occurred with low frequency, we used Fisher's exact test.

$P < 0.05$ was regarded as statistically significant. Results are presented as mean and standard deviation.

RESULTS

Patient variables

There were no significant differences between the four groups regarding age, weight, height and the duration of surgery (table I).

Sensory blockade

There were no significant differences between the four groups for the time to onset of analgesia (table II). However, analgesic blockade spread more quickly in the patients treated with larger doses of opioid.

The average regression times of −2S and −4S, and the time of disappearance of analgesia from the last thoracic dermatome (−T12), were not altered in patients treated with lower doses of opioid (B:F 50 *v.* B:F 0 and B:F 100 *v.* B:F 0—$P < 0.05$), but were significantly prolonged in patients treated with larger doses of fentanyl (B:F 200 *v.* B:F 0; B:F 200 *v.* B:F 50; B:F 200 *v.* B:F 100—all $P < 0.05$).

In contrast to this favourable effect of prolonged duration of analgesia, we noted, with increasing doses of the opioid, a decrease of penetrability of the anaesthetic solution to the large spinal roots (S1). The missing of this segment increased progressively with increasing concentration of opioid and reached the greatest value (65%) in patients treated with fentanyl 200 µg ($P < 0.05$; test for linear trend in proportions).

Data summarizing the spread and duration of analgesic blockade are shown in figure 1.

Motor blockade

Subjective latency appeared to decrease progressively with increasing doses of fentanyl (Spearman correlation test: $r = -0.468$; $P < 0.001$). However, there was no statistically significant decrease in latency of objective partial or complete motor blockade or of the time taken to achieve complete spread (table III). Likewise, there was no difference between the various groups with regard to either subjective and objective evaluation of the duration of the blockade, or time to complete spread.

The intensity of the motor blockade assessed by myotome score was significantly lower ($P < 0.02$) in the patients treated with larger doses of fentanyl (group B:F 200), in whom the myotome score differed significantly from the other groups after about 25 min (fig. 2), the difference increasing in the subsequent observations.

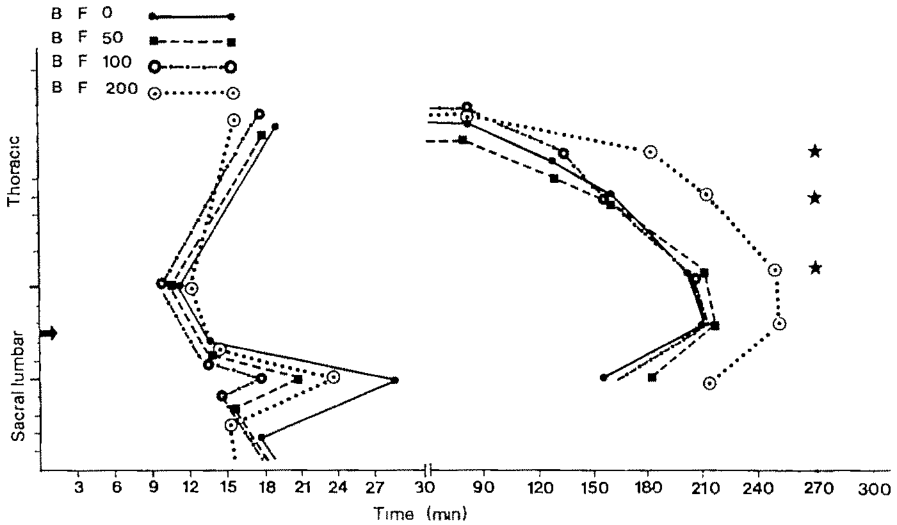

FIG 1. Mean time-segment diagram for sensory blockade. Data points plotted are mean values. → Site of injection of local anaesthetic–fentanyl mixtures. *Significant difference among groups ($P < 0.05$).

TABLE III. *Motor blockade (mean values SD)). *Probability of significant difference among groups (ANOVA, Kruskal–Wallis test) †Spearman correlation test for subjective onset as a function of the concentrations of fentanyl: r = −0.468; P <0.001*

	Group B.F0	Group B:F50	Group B:F100	Group B:F200	*P**
Subjective onset (min)	8 (4)	8 (3)	7 (2)	4 (2)	<0.01†
Onset of partial motor block (min)	15 (5)	17 (6)	18 (6)	18 (12)	ns
Onset of complete motor block (min)	20 (7)	24 (8)	25 (10)	18 (5)	ns
Complete spread (min)	31 (13)	31 (7)	32 (10)	24 (12)	ns
Maximum score assessed (myotome score)	7.30 (3.95)	6.80 (5.21)	7.23 (3.42)	3.85 (3.39)	<0.02
Objective motor block duration (min)	161 (56)	141 (57)	143 (64)	138 (48)	ns
Subjective motor block duration (min)	235 (63)	219 (69)	211 (74)	215 (35)	ns

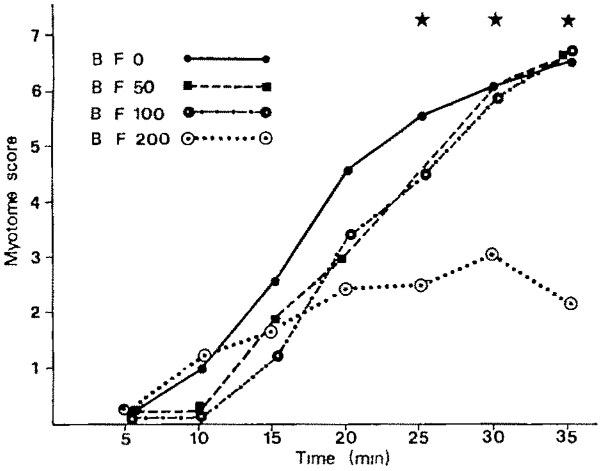

FIG 2. Mean time–myotome score at each time interval after administration of extradural blockade (maximum possible score = 16, i.e. eight for each right and left side). *Significant difference among groups ($P < 0.05$).

Haemodynamic and respiratory effects

In all the groups, systolic pressure was reduced significantly after extradural blockade. The addition of an opioid agent did not increase the cardiovascular depression; on the contrary, in patients receiving fentanyl, hypotension developed more gradually (table IV), and there were fewer patients with systolic pressures less than 100 mm Hg (table V) or requiring medication for acute hypotension (table VI).

There was no significant difference between the groups with regard to heart rates (table V), but respiratory rate decreased significantly ($P < 0.05$) in the B:F 200 group (table V). Obvious respiratory depression, either early or late, did not occur and no patient required an opioid antagonist.

Side effects

The side effects noted during and immediately after surgery are shown in table VI and VII. Increased doses of extradural opioid resulted in more drowsiness during operation and, in general, the opioid-treated patients were more sedated than the patients in the control group. Drowsiness was reduced by simple verbal stimuli and did not cause amnesia.

Shivering did not occur in the B:F 200 group, and only one of those patients suffered acute hypotension (table VI). The addition of opioid had little influence on the incidence of headache, and fentanyl did not appear to affect the frequency of nausea and vomiting (table VII).

The only positive finding was a reduction of dizziness after operation in the groups which received fentanyl. Itching occurred only in the fentanyl groups (17%) and was most frequently noted 1–6 h after surgery. These patients experienced varying degrees of pruritus, which was usually mild and confined to the anterior chest, groin, nose and face (in order of frequency). The difference between the treated and the control groups was significant ($P < 0.05$), but a relationship between this side effect and increasing dose of opioid could not be demonstrated.

Micturition difficulties were recorded in both the fentanyl and control groups; there was no statistically significant difference between the four groups. Nevertheless, it was clinically significant that the

TABLE IV *Change in systolic arterial pressure (mm Hg) after administration of extradural blockade (mean values (SD))*

Group	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min
B:F 0	+6 (60)	−8 (19)	−14 (22)	−25 (21)	−24 (23)	−27 (25)	−26 (24)	−24 (23)
B:F 50	−6 (13)	−12 (22)	−20 (30)	−18 (21)	−15 (24)	−19 (25)	−17 (25)	−16 (21)
B:F 100	−4 (19)	−13 (27)	−21 (29)	−23 (29)	−21 (23)	−14 (21)	−13 (22)	−14 (24)
B:F 200	+1 (11)	−11 (23)	−20 (26)	−25 (30)	−23 (24)	−24 (23)	−25 (19)	−25 (21)

TABLE V. *Haemodynamic and respiratory effects. *Probability of significant differences among groups (Kruskal–Wallis test, chi sqaure test)*

	Group B:F 0	Group B:F 50	Group B:F 100	Group B:F 200	*P**
Mean decrease (SD) in systolic pressure from preoperative value (mm Hg)	−38 (22)	−34 (23)	−34 (23)	−36 (22)	ns
Number of patients with systolic pressure less than 100 mm Hg	6/20	3/20	3/20	3/20	ns
Mean decrease (SD) in heart rate from preoperative value (beat min^{-1})	−11 (10)	−6 (8)	−10 (14)	−11 (12)	ns
Mean decrease (SD) in respiratory frequency from preoperative value (b.p.m.)	−2 (2)	−1 (3)	−1 (2)	−3 (2)	<0.05

TABLE VI. *Occurrence of side-effects during surgery (No. patients). *Probability of significant difference among the groups (chi square test) †Significant difference* (P <0.02) v. *other groups (Fischer's exact test, one-tailed). ‡Significant difference* (P=0.053) v. *control groups (Fischer's exact test; one-tailed)*

	Group B:F 0	Group B:F 50	Group B:F 100	Group B:F 200	*P**
Shivering	6/20	8/20	5/20	0/20†	<0.025
Need for supplementary analgesic medication	1/20	0/20	0/20	0/20	ns
Drowsiness	0/20	1/20	2/20	4/20‡	ns
Acute hypotension	4/20	2/20	4/20	1/20	ns

only patients who needed catheterization of the bladder belonged to the groups receiving fentanyl. In three patients in the B:F 200 group, we avoided catheterization by giving naloxone 0.4 mg i.v. 8 h after surgery. Intestinal transit was delayed in patients treated with larger doses of opioid (group B:F 200). The percentage of patients who resumed some form of intestinal transit within the first 24 h was 5% in the B:F 200 group and 56% in the other groups ($P < 0.05$).

The patient's opinion

The addition of opioid to the anaesthetic solution did not change the clear preference of all the patients for extradural analgesia (table VIII). Thus, side effects, when present, were of limited importance or were indeed of a positive nature. For example, a patient who had been treated first with bupivacaine alone, and later with an opioid–anaesthetic mixture (in group B:F 100), stated that he preferred the latter technique, on account of less shivering and greater sedation. In one instance of negative opinion, this may have been induced by a complication (dural tap), and in two other patients it may have been caused by the long period of observation.

DISCUSSION

There are three main conclusions from our studies:

(1) Mixtures of bupivacaine and fentanyl prolonged the analgesic blockade only when larger doses of opioid (200 μg) were used. Smaller doses (50 and 100 μg) had no effect.

TABLE VII. *Occurrence of side-effects after operation (No. patients). §Only patients undergoing herniorraphy. *Probability of significant difference among the groups (chi square test). †Significant difference* v. *control groups (Fischer's exact test, one-tailed). ‡Significant difference* (P <*0.05)* v. *other groups (Kolmogorov–Smirnov test, one tailed)*

	Group B:F 0	Group B:F 50	Group B:F 100	Group B:F 200	*P**
Dizziness	4/20	2/20	1/20	0/20	ns
Headache	3/20	2/20	3/20	3/20	ns
Nausea or vomiting	2/20	4/20	2/20	4/20	ns
Itching	0/20	2/20	6/20†	2/20	<0.05
Difficulty in micturition§	3/10	8/14	4/13	7/15	ns
Bladder catheterization§	0/10	2/14	1/13	1/15	ns
Onset of intestinal transit after operation.					
0–24 (h)	10	10	13	1‡	
24–28 (h)	8	8	3	10	
48–72 (h)	2	1	4	9	<0.01

(2) As the dose of narcotic increased, the anaesthetic solution lost ability to block the motor fibres and the 1st sacral segment (S1).

(3) The opioid–local anaesthetic mixtures appeared able to modify the response of the autonomic nervous system to extradural blockade. For example, the patients treated with higher doses of fentanyl exhibited fewer episodes of acute hypotension, and none shivered.

Onset and duration of analgesia from both fentanyl and bupivacaine are similar. When fentanyl is injected alone to the extradural space, analgesia appears within 10 min (Lomessy, Viale and Motin, 1981; Devaux et al., 1982: Pierrot et al., 1982) and lasts about 3 h (McQuay et al., 1980; Rutter, Skewes and Morgan, 1981; Pierrot et al., 1982; Rucci et al., 1983). One might expect, therefore, that small doses of fentanyl (50–100 μg) would not modify the analgesic blockade of bupivacaïne. However, it is likely that, as is the case with morphine (Yaksh et al., 1979; Pybus and Torda, 1982), the duration of analgesia from fentanyl is dose-dependent. Larger doses may cause prolonged depression of wide-dynamic-range (WDR) neurones (Suzukawa et al., 1982) with consequent medullar inhibition of the nociceptive input. It is unlikely that the enhancement of the analgesic blockade from bupivacaine occurs only when the opioid concentration in the extradural space becomes sufficiently high to cause a local anaesthetic effect. This has been

TABLE VIII. *Patients' opinions of anaesthetic procedures (No. patients). *Probability of significant difference among groups (chi square test). †In one patient, dural tap and blood patch 5 days after surgery*

	Group B:F 0	Group B:F 50	Group B:F 100	Group B:F 200	%	P*
Subject submitted to previous anaesthesia:	13/20	8/19	9/20	8/20	47	ns
General anaesthesia	13	3	8	8		
Regional anaesthesia	2	5	2	0		
Considered anaesthetic technique:						
Very adequate	16	17	18	15	96	ns
Adequate	3	2	2	3		
Inadequate	1	0	0	2†		
Wishes for eventual future surgery:						
Same anaesthesia	17	18	17	17	94	ns
Undecided	1	1	2	1		
Different anaesthesia	2	0	1	2†		

demonstrated for meperidine (Cousins et al., 1979; Raj et al., 1983), but not for morphine (Bullingham et al., 1983). Furthermore, an hypothetical enhancement of local anaesthetic action at membrane level would hardly agree with a weakening of the motor blockade, with the increasing failure to block S1 completely, and with fewer involuntary phenomena (acute hypotension and shivering) observed in the fentanyl-treated groups. These observations suggest, on the contrary, greater passage of impulses along both larger and smaller fibres, and agree with experimental data which showed that opioids can enhance the excitability of presynaptic terminals of Aδ and C primary afferents (Jurna and Grossmann, 1977; Sastry, 1978; 1979) and of some non-nociceptive dorsal horn neurones (Dostrowsky and Pomeranz, 1976; Belcher and Ryall, 1978; Randic and Miletic, 1978). It has also been demonstrated (Raj et al., 1983) that morphine and fentanyl, in low doses, seemed to potentiate peripheral nerve conduction of Aα, and to a lesser extent of Aδ, action potentials.

It has been known for a long time (Gergis, Hoyt and Sokoll, 1971) that fentanyl given i.v. can cause rigidity of the trunk and extremities (Stanley and Webster, 1978; Comstock, Scamman and Carter, 1979; Comstock et al., 1981; Hill et al., 1981). The cause of this rigidity is not clear, but it could be related to an increase of monosynaptic spinal reflexes (Sokoll, Hoyt and Gergis, 1972). In any case these observations are consistent with the reduction of the motor blockade in patients treated with larger doses of opioid. It is unlikely that the observed effects were the result of the insignificant increase in the injected volume and consequent decrease of bupivacaine and adrenaline concentrations; all patients had the same dose of these drugs and the mass of injected drug, rather than volume, is the predominant factor in the spread and characteristics of extradural blockade (Bromage et al., 1964; Bromage, 1975; Thorburn and Moir, 1981).

The addition of fentanyl to the anaesthetic solution caused no serious complications. The only side effects of any relevance were itching and bladder dysfunction. The precise neurological basis for itching is still uncertain (Bromage et al., 1982b); perhaps it is derived from a facilitatory action by opioid agents on non-nociceptive neurones in the dorsal horn (Belcher and Ryall, 1978). Difficulty or incapacity to empty the bladder is one of the most frequent side effects attributed to extradural opioids. This undesirable effect is more common after morphine (Weddel and Ritter, 1981; Peterson et al., 1982) than after fentanyl (Devaux et al., 1982). We observed micturition difficulties in 45% of our groups receiving fentanyl, although bladder dysfunction was common (30%) also in patients receiving extradural anaesthesia with anaesthetic solution alone.

Dundee (1980) has suggested that, when patients are questioned about their opinions on the anaesthetic technique as ours were, the technique should receive overall, 80–85% satisfied and only about 5% dissatisfied responses in order to be acceptable clinically. On this basis, our results suggest that extradural anaesthesia with a mixture of anaesthetic solution and fentanyl had the same high degree of acceptability as extradural blockade performed with bupivacaine alone. This reflects that the side effects were of minor importance or were of a positive nature.

In conclusion, there are both advantages and disadvantages in adding fentanyl 200 μg to 0.5% bupivacaine 20 ml with adrenaline 1:200 000 for lumbar extradural blockade. The advantages are: shorter time of spread and greater duration of analgesic block; better sedation during operation and reduction of episodes of shivering and acute hypotension. The disadvantages are a reduction of motor blockade, greater occurrence of incomplete blockade of the 1st sacral segment, occasional appearance of itching and bladder dysfunction after surgery, and delayed intestinal transit. Smaller doses of fentanyl do not offer significant differences compared with use of anaesthetic solution alone.

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LUMBAR SYMPATHECTOMY: A SINGLE NEEDLE TECHNIQUE

V. S. HATANGDI AND R. A. BOAS

SUMMARY

A single-needle lumbar sympathectomy technique is described which uses the tip of the 12th rib as a marker to determine the appropriate position for the insertion of the needle. Radiological screening is used to control final placement at the body of L3 and to visualize spread of radio-opaque phenol in the correct prevertebral plane. Following sympathectomy, fore-foot temperatures increased by a mean of 3 °C and lower leg blood flow doubled, these being accompanied by significant increases in ankle pressure index and venous oxygen tensions in the affected foot. These physiological improvements brought about resolution of ischaemic foot pain in 70% of patients at follow up 1 month later. As these results were not significantly different from those obtained in patients having two-needle sympathectomy, blockade with a single needle under x-ray control is considered to be an effective technique for the performance of neurolytic sympathectomy.

The benefits of neurolytic lumbar sympathectomy in the treatment of peripheral vascular disease and reflex sympathetic dystrophy are well established (Löfstrom, Lloyd and Cousins, 1980; Boas and Hatangdi, 1983). Procedural improvements following the introduction of x-ray control by Reid, Watt and Gray (1970), and the later use of radio-opaque neurolytic solutions with fluoroscopic monitoring (Boas, Hatangdi and Richards, 1976) have made possible the immediate visualization of the position of the needle and the spread of the neurolytic solution during injection. Thus, on account of its greater safety and certainty, this technique (neurolytic sympathectomy) has superseded surgical sympathectomy in many centres.

Previous reports have advocated the use of a two- or three-needle technique with insertion of the needle commencing variously 8–12 cm lateral to the vertebral spines. The extent of lateral placement has usually been determined by a global assessment of body size, larger patients requiring the wider needle placement. This paper describes a single needle approach using the patient's bony landmarks to determine the appropriate position for insertion of the needle. Further, the results of sympathectomy undertaken by this method are compared with a two-needle technique.

PATIENTS AND METHODS

Patients

A total of 508 patients who underwent chemical lumbar sympathectomy provide the material for this study. Of these, 318 received blockade using a single needle, while 290 patients, most from our earlier series, received sympathetic blockade using two needles. There were no differences between the two groups on the basis of age, sex or disease distributions (mean age 71 ± 11 yr; arteriosclerotic disease in just over 90%).

Techniques of sympathetic blockade

Two-needle. An essential pre-requisite of consistent accuracy in the performance of sympathetic blockade, is the use of a mobile C-arm x-ray screening facility, to allow correct placement of the needle and to monitor the spread of 7% phenol in radio-opaque solution (Boas and Hatangdi, 1983). With the patient lying prone under light sedation, local anaesthetic was infiltrated to the skin and deeper tissues, 8–10 cm lateral to the midline at the level of the L3 and L4 vertebrae. The needles (stiletted 20-

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gauge) were inserted lateral to the transverse processes, to reach the ventrolateral aspect of the mid portion of L3 and L4 vertebral bodies. Critical to the success of this method is the placement of each needle tip within 0.5–1 cm of the lateral margin of the vertebral bodies (fig. 1). In a lateral projection the needle tips must lie at the level of the ventral border of each vertebra so that the neurolytic solution is dispersed in the correct prevertebral tissue plane. After negative aspiration and confirmation of correct spread of contrast solution, the full volume (3–5 ml at each level) is injected until the desired extent of spread is attained.

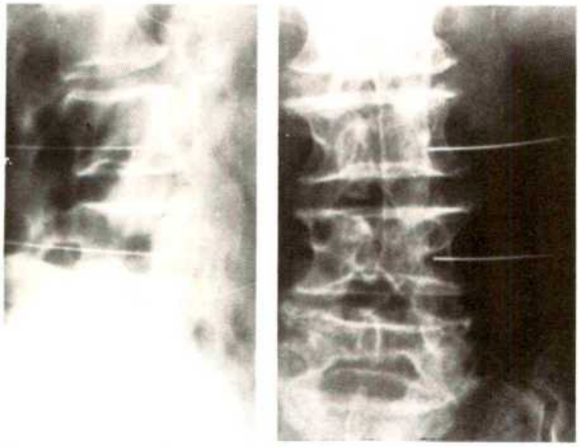

FIG. 1. X-rays of correct needle placement in A–P and lateral projections for lumbar sympathectomy. The single needle method requires only the upper needle at L3. Note also, the proximity of the aorta as outlined by its extensive calcification in this patient.

Single-needle. Preparation and positioning of the patient are as for the two-needle method. The midline is marked and the tip of the 12th rib palpated on the side to be injected. A point 2–3 cm below and medial to the tip of the rib is marked as the site for insertion of the needle. This point of entry will be opposite the body of the 3rd lumbar vertebra as marked in figure 2.

Slim patients may require an entry point 6.5 cm from the midline, while in broader patients this may be up to 15 cm. Use of a 12-cm long needle is sufficient for most patients, but where wider placement is required 15-cm needles are needed to achieve adequate depth of insertion. Final placement at a mid-L3 level uses the same landmarks as for the two-needle technique. When correctly positioned, spread of neurolytic radio-opaque phenol solution over two to three vertebrae is achieved easily with a volume of 8–12 ml (fig. 3).

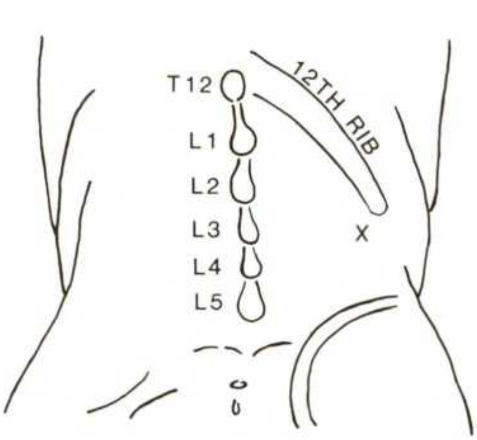

FIG. 2. Schematic diagram showing the site of needle insertion (×) using the tip of the 12th rib as a marker.

Patient assessment

Patients in both groups were evaluated before and 1 h after blockade, and 1 month later. Assessments were made of clinical and objective measures of response to treatment.

Clinical responses. Subjective changes of relief from rest pain, improvement in skin temperature and colour, and the extent of healing of ulcers were recorded.

Objective testing. In all patients, skin temperatures were taken from the affected fore-foot and from the contralateral side, using thermistor probes fixed bilaterally to record control values (before sympathectomy) and at the subsequent 1 h. More detailed studies were undertaken in a smaller group of 27 patients, 15 of whom received one-needle and 12, two-needle blocks. Measurements of lower leg blood flow utilized strain gauge plethysmography, using the method of Sumner (1978). Systolic pressure differences (pressure index) between arm and ankle (posterior tibial) were also taken using Doppler flow probes. Venous oxygen tensions were measured in blood samples drawn from indwelling catheters in the dorsum of the affected foot. Approximately one-half of this smaller group were also available for repeat studies at a further follow-up, 1 month after sympathectomy. Tests were undertaken in the same room on every occasion, with the ambient temperature controlled to 20 °C in an air-

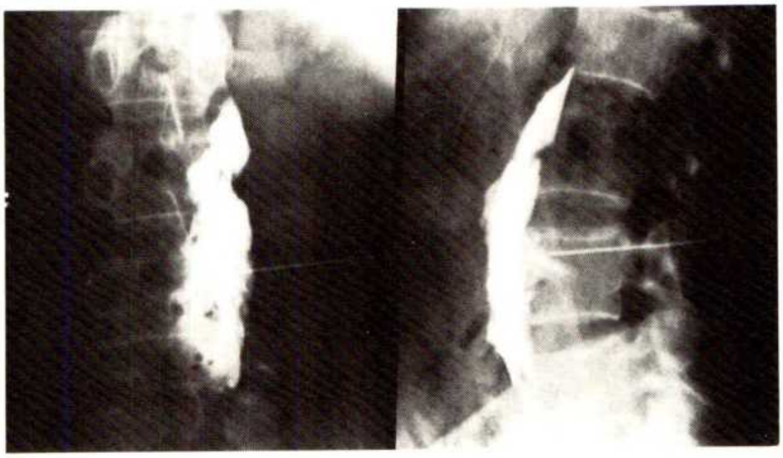

FIG. 3. Extent of phenol spread in A–P and lateral projections using 10 ml of solution with a one-needle technique.

conditioned environment.

RESULTS

In a recovery room setting, monitoring and evaluation of patients was continued for at least 1 h following sympathectomy. No adverse cardiovascular or symptomatic responses were noted in any patient over this period. Changes in mean cutaneous temperature are given in table I, together with the detailed physiological recordings taken from small but representative groups of patients selected for study. The affected foot of patients from the one-needle group showed a significantly greater increase in mean temperature (3.2 °C) than the two-needle group (2.2 °C). Further analysis (table I) showed that 68% of patients following the one-needle and 61% of patients undergoing the two-needle technique had increases in temperature greater than 1 °C, although, statistically, these values were not significantly different.

Limb blood flow was approximately doubled in both groups 1 h after sympathectomy. This was paralleled by considerable improvement in venous oxygen tensions and systolic pressure measurement at the ankle in both groups. Comparison of these results showed no statistically significant differences between the one- and two-needle techniques (unpaired Student's *t* test). Because it was not possible to obtain both of these measurements in all patients, as a result of the wide scatter of results, any attempt to draw inferences from these data are precluded.

From a clinical standpoint, the most important result (table II) was the level of improvement in pain, ulceration and ischaemic change noted at the 1-month follow-up. Over 70% of patients in each group showed resolution of pain, while healing of

TABLE I. *Changes (mean ± SD) from control values 1h after sympathectomy*

	Number studied	One-needle	Two-needle
Increase in skin temp (°C)	508	3.2±3.6	2.2±3.1
Increase >1°C	508	68%	61%
Increase in systolic AP (mm Hg)	22	11.5±38	22.7±29
Increase in limb blood flow (%)	27	87.8±111	150.5±154
Increase in venous oxygen (kPa)	25	3.16±1.97	2.30±2.24

TABLE II. *Changes (mean ± SD) from control values 1 month after sympathectomy*

	Number studied	One-needle	Two-needle
Patients with symptomatic resolution	403	77%	73%
Patients with groin dysaesthesia	403	5%	7%
Increase in skin temp (°C)	18	1.6±2	3.7±4
Increase in systolic AP (mm Hg)	11	19±45	26.5±43
Increase in limb blood flow (%)	16	110±316	77±109
Increase in venous oxygen (kPa)	6	0.75±2.5	2.63±0.92

ischaemic ulceration occurred in 50%—equally for one- or two-needle techniques. Improvements in blood flow and posterior tibial pressures were sustained, but data were insufficient to compare oxygen tensions. Temperature responses tended to decrease by approximately 50%, although some distortion was brought about because more patients with vasospastic disease returned for follow-up in the two-needle group.

With the level of insertion used for the single needle technique, no procedural complication such as major organ penetration was recognized in any of the patients. The only complication observed in this series of 508 patients was the occurrence of groin dysaesthesia in 5% of patients undergoing one-needle and 7% of patients undergoing two-needle sympathectomy. This usually started about 1 week after blockade and reached peak intensity at about 2–3 weeks. No sensory deficit was found in these patients, nor did reassessment of radiographic films show any patient with excessive lateral or dorsal spread of dye, which could have involved the segmental somatic nerve supply. Resolution occurred in every patient, usually spontaneously within 4–6 weeks, although a few of the more severe cases were treated successfully with anticonvulsant drugs or transcutaneous electrical stimulation.

DISCUSSION

It was noticed frequently in the course of performing two-needle sympathectomy, that satisfactory spread of radio-opaque phenol solution could be produced by injection through only one of the needles. This led to a closer examination of the merits of a single-needle technique. The two patient groups studied were not strictly comparable, because the majority of the two-needle sympathectomies took place chronologically earlier and may, therefore, have been performed with a lower level of proficiency. Even so, the results of blockade in the two patient groups suggest that there is no difference in outcome between one- or two-needle techniques. On this basis, a single-needle sympathectomy confers some advantage. It causes less patient discomfort, allows quicker performance of the blockade and requires less exposure to radiation. The study further confirms the nature and extent of responses to sympathectomy as reported by Cousins, Reeve and Glyn (1979) and reviewed by Bonica (1980–81). It is not the purpose of this paper to discuss the merits or implications of the various physiological measures, this being the basis for future communication.

The anatomical and clinical objective in providing optimal needle placement for sympathectomy, is to ensure accuracy of the dispersement of the solution within the prevertebral tissue plane containing the sympathetic chain. A critical factor in achieving this accuracy is a sufficiently lateral position for needle insertion. Reid, Watt and Gray (1970) emphasized the need to avoid the lumbar transverse process and allow a quicker and less painful injection. Using this approach, the risk of renal and ureteric puncture is almost negligible (Cherry and Rao, 1982). Anatomical studies by these authors further confirmed the greater efficacy of sympathetic ablation with an adequately lateral needle insertion. In these and previous reports, however, a predetermined fixed distance from the midline has been used as the point of entry. In some patients, especially those who were overweight, this led to a more vertical needle entry, and consequently, solution was placed in the plane of the psoas fascia, lateral to the vertebral body and the sympathetic chain and with an attendant risk of damage to somatic nerves. The method adopted in this study has utilized the tip of the 12th rib, which will, in most patients, act as a landmark which provides an appropriately lateral placement of the needle according to the bony morphology of the patient. However, the variability of the 12th rib in a proportion of patients requires that this technique be used in conjunction with fluoroscopic control, for both practical and legal considerations. Accuracy of blockade is enhanced, and the subsequent x-ray of the spread of the radio-opaque solution provides a graphic record of the procedure. On the basis of these criteria, the single-needle technique is offered as one giving improved patient comfort with greater facility and safety in the performance of effective lumbar sympathectomy.

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SUBARACHNOID BLOCKADE AND TOTAL HIP REPLACEMENT

Effect of Ephedrine on Intraoperative Blood Loss

J. THORBURN

SUMMARY

Thirty-eight patients undergoing total hip replacement under subarachnoid blockade were allocated randomly to one of two groups. Following institution of the blockade, patients in group A received ephedrine i.v. to maintain the systolic arterial pressure at, or above 100 mm Hg. Patients in group B were managed in an identical way, but did not receive ephedrine. Significant differences in arterial pressure (P < 0.001), and heart rate (P < 0.005), but no significant difference in blood loss was observed in the two groups. This was confirmed by similar blood transfusion requirements and postoperative haemoglobin concentrations. The relevance of the use of pressor agents in spinal anaesthesia is discussed.

Subarachnoid blockade is associated with a decrease in blood loss during operation, and may be advantageous in operations such as total hip replacement in which blood loss may be substantial. Although decreases in systemic arterial pressure frequently accompany subarachnoid blockade, the optimum reduction in arterial pressure is controversial, particularly in an elderly population, and the relationship between systemic hypotension and blood loss is not clear (Moir, 1968; Sculco and Ranawat, 1975). In the U.S.A. it is usual to prevent such hypotension – by the use of pressor agents, if necessary (Greene, 1969). Sculco and Ranawat (1975), using subarachnoid blockade and with active management of the hypotension noted a decrease in intraoperative blood loss of 50% when compared with that observed in patients receiving general anaesthesia for total hip replacement. However, this decrease was almost identical to that noted in a similar study, with the exception that the hypotension resulting from the block was not treated (Thorburn, Louden and Vallance, 1980).

This study was undertaken to examine the effect of the administration of ephedrine on intraoperative blood loss in patients undergoing total hip replacement under subarachnoid blockade.

PATIENTS AND METHODS

Patients admitted for total hip replacement were allocated randomly (by drawing a card without replacement) to either group A ($n = 19$; 15 female) or group B ($n = 19$; 17 female). Patients in group A received ephedrine i.v. following the induction of the subarachnoid blockade, the dose of ephedrine injected being that amount required to maintain the systolic arterial pressure greater than 100 mm Hg. Apart from the injection of ephedrine, both groups of patients were treated identically. Informed consent was obtained and each patient was premedicated with nitrazepam 5–10 mg by mouth, 90 min and morphine 5–10 mg i.m., 60 min before the operation. In the anaesthetic room, the dose of sedation was adjusted using droperidol 1–3 mg and pentazocine 5–10 mg i.v. to render the patient drowsy but rousable. The heart rate and arterial pressure were recorded when the sedation was deemed to be adequate. The patient was turned to lie on the affected side, with a 10–15° head-up tilt. Using a midline approach, the spinal puncture was made with a 25-gauge needle. Clear CSF was obtained before and after the slow injection of cinchocaine 2–3 ml in 6% glucose, the dose depending on the height of the patient. This position was maintained for at least 6 min, until evidence of motor blockade was apparent. The patient was then placed in the modified supine position, with a wedge positioned under the affected hip, and the operating table level-

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led after 5 min. When evidence of motor blockade had been obtained and a decrease in arterial pressure observed, ephedrine 5–10 mg was injected i.v. (group A), to achieve an arterial pressure of greater than 100 mm Hg. The maximum height of the blockade achieved could not be determined readily, as a laminar flow operating room was used, and this precluded easy access to the patient.

Arterial pressure was measured using an oscillotonometer and the ECG and heart rate (photoelectric probe) were monitored continuously. The arterial pressure was monitored frequently following institution of the block, but was recorded at 15-min intervals (as was heart rate). Ephedrine was injected as required to maintain the systolic arterial pressure at greater than 100 mm Hg.

Before surgery all patients had the following routine investigations performed: chest x-ray, electrocardiogram, and measurement of serum electrolyte, creatinine and haemoglobin concentrations. The biochemical and haematological investigations were repeated 72 h after surgery.

Only patients presenting for primary operations were selected; no patient who had previous operations on the affected hip was included in the study, and only Muller or Charnley arthroplasties were performed.

Blood loss during operation was measured gravimetrically and added to the blood loss measured in the suction bottles. The wound drainage was that obtained and measured from the wound suction drain following surgery.

Results were analysed using Student's *t* test, or Chi-squared test as appropriate.

RESULTS

There were 19 patients in each group, and table I shows the data obtained before operation in the two groups. No significant differences were observed between the two groups. The serum creatinine concentration was increased, but not significantly in group A. The population was predominantly elderly, with a mean age of 64 yr. Six of the patients were males. Considerable variation in preoperative systolic arterial pressures was noted, confirming the relative frequency of hypertension (Alexander and Barron, 1978).

Following the induction of subarachnoid blockade, patients in group A received a mean of ephedrine 23.7 mg i.v. (table II), and the mean systolic arterial pressure observed throughout surgery was 107 mm Hg. This was significantly greater than that observed in patients in group B (88 mm Hg) ($P < 0.001$), the percentage decreases in the systolic pressures from their preoperative values being 20.3% and 34.6%, respectively. The blood loss measured during surgery was not significantly different in the two groups (481 ± 136 ml in group A and 545 ± 226 ml in group B). The heart rate during operations in patients receiving ephedrine was 81 beat min^{-1}, a significant increase ($P < 0.005$), from that observed in patients who did not receive ephedrine (67 beat min^{-1}).

TABLE I. *General details of the patients studied, including haematological and biochemical data (mean values ± SD). Differences between the groups are not significant*

	Group A (ephedrine)	Group B
Number of patients	19	19
Number of females	15	17
Mean age (yr)	65.31 ± 9.6	63.94 ± 10.15
Mean height (cm)	160.64 ± 10.03	159.08 ± 8.15
Mean wt (kg)	60.78 ± 10.08	58.87 ± 11.94
Hb (g dl^{-1})	12.98 ± 0.89	13.41 ± 1.11
Serum creatinine concn (μmol litre^{-1})	91.44 ± 29.9	79.37 ± 18.9
Number of Muller arthroplasties	14	13

TABLE II. *Intraoperative details, including blood loss, arterial pressure and heart rate (mean values ± 1 SD). *P < 0.001*

	Group A (ephedrine)	Group B
Blood loss (ml)	480.94 ± 135.79	544.47 ± 226
Systolic AP (mm Hg)	107.17 ± 9.34	87.60 ± 15.19*
Heart rate (beat min^{-1})	81.42 ± 13.31	66.92 ± 12.4*
% Change in AP (from pre-anaesth.)	20.30 ± 11.67	34.57 ± 13.5
Dose of ephedrine (mg)	23.68 ± 11.69	

In the period after operation, the volume of blood obtained from the wound suction drain was similar in both groups (table III); 607 ± 234 ml in patients in group A and 684 ± 228 in group B. No significant change was observed in the serum creatinine concentrations on the 3rd day when compared with those measured before surgery and between groups, but the haemoglobin concentration on the 3rd day had decreased substantially in both groups, to 10 ± 1.4 g dl^{-1} in patients in group A, and to 10.3 ± 1.4 g dl^{-1} in patients in group B (ns). Two patients in each group received a blood transfusion. One patient in each group received one unit of blood during surgery, and the other two patients, also one in each group, were each transfused two units in the period after operation.

TABLE III. *Postoperative wound drainage, haemoglobin concentration and serum creatinine concentration (mean values ± 1 SD)*

	Group A (ephedrine)	Group B
Hb (g dl^{-1})	9.99 ± 1.38	10.25 ± 1.40
Serum creatinine concn (μmol $litre^{-1}$)	88.91 ± 22.31	80.15 ± 18.62
Wound drainage (ml)	606.67 ± 234.18	684.18 ± 227.65

No significant correlation was observed between either the percentage change in arterial pressure and blood loss ($r = 0.3568$) in patients in group B, nor between weight and blood loss ($r = 0.1445$).

DISCUSSION

These results demonstrate that there was no increase in blood loss during total hip arthroplasty under subarachnoid blockade in patients receiving ephedrine i.v., although substantial differences in cardiovascular haemodynamics were observed. The similarity of the volumes obtained from the wound suction drain, and of the haemoglobin concentrations measured following surgery confirm the absence of substantial differences in blood loss during surgery.

An attempt was made to decrease the number of variables in the study by limiting entry to patients having first operations, and only two types of operation were performed, the numbers of each type of operation being similar in each group. This ensured that the duration of surgery was also similar, as it has been claimed that blood loss is related to the duration and type of surgery (Amaranath et al., 1975).

With modest doses of anaesthetic agent, and a limited degree of blockade, an increase in lower limb blood flow was observed (Berenyi, Shimasato and Etsten, 1964). As the height of the blockade is increased, there is a progressive decrease in arterial pressure and at some point, equivalent to a systolic arterial pressure of 90 mm Hg (Greene, 1969), the venous return is decreased with a consequent decrease in cardiac output. Clearly, a possible explanation for a decrease in blood loss would be a decrease in cardiac output. Spinal blockade to T5 and ephedrine i.v., produces a 10% decrease in peripheral resistance and increase in cardiac output, indicating an increase in venous return (Ward et al., 1966). The 23% difference in arterial pressure and the 22% difference in heart rate observed between the two groups were the result of haemodynamic changes which might have, as a consequence, differing blood losses. Failure to demonstrate a significant correlation between the percentage change in arterial pressure and intraoperative blood loss suggests that the mechanism of the reduction in blood loss associated with subarachnoid blockade is not related to the haemodynamic changes in the cardiovascular system.

The precise reason for the decrease in blood loss with subarachnoid blockade is not clear. Individual differences in blood loss can be attributed to variables such as obesity, or to difficulties associated with the operation, and these can account for the relatively large standard deviation. Moir (1968) suggested that the decrease in blood loss was consequent upon the sympathetic block decreasing venous pressure, and permitting the slight gravitational forces to empty the veins. Clearly, the use of ephedrine does not influence this mechanism.

The safety of subarachnoid blockade has been noted in several North American studies (Vandam and Dripps, 1955; Noble and Murray, 1971), and current teaching is to prevent arterial hypotension (Cousins and Bridenbaugh, 1980; Miller, 1981). If subarachnoid blockade decreases the arterial pressure by 10–15%, measures should be taken to increase the pressure by adopting the Trendelenberg position, by increasing the rate of the infusion of fluids i.v., and by the use of pressor agents (Greene, 1969). It has been suggested that elderly patients do not withstand the decrease in arterial pressure as readily as younger patients. Comparable studies have not been undertaken in the U.K., but current teaching is less rigid in the approach to the control of arterial pressure (Churchill-Davidson, 1978). When the blockade extends above T5, bradycardia is relatively common (Kennedy et al., 1970), and requires treatment. Although in the present study an attempt was made to limit the spread of anaesthetic agent by utilizing the position of the patient and time, the degree of hypotension would suggest that the block was extensive.

The safety of subarachnoid blockade has been questioned in an elderly population (Dennison, 1979). If the concomitant use of pressor agents is associated with the advantages of subarachnoid blockade, namely the decrease in blood loss, yet avoids the onset of bradycardia and profound arterial hypotension, it may be an advantage to use pressor agents more frequently in the treatment of hypotension.

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COMPARISON OF MIDAZOLAM, DIAZEPAM AND PLACEBO I.M. AS PREMEDICATION FOR REGIONAL ANAESTHESIA

A Randomized Double-Blind Study

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SUMMARY

In a randomized double-blind study, midazolam 0.1 mg kg^{-1} i.m. was compared with diazepam 0.2 mg kg^{-1} and placebo as premedication for patients undergoing urological interventions under spinal anaesthesia. The sedative and anxiolytic effects of midazolam were evident 5–10 min after administration, and were maximum between 30 and 90 min. After this, rapid recovery was observed. More than 90% of the patients receiving midazolam were totally or partially amnesic for the procedures in the induction room and the operation theatre. Amnesia was not seen in the patients receiving diazepam or placebo and, in contrast to midazolam, diazepam had almost no sleep-inducing effect. In a few patients, the depth of sleep achieved with midazolam 0.1 mg kg^{-1} was such that co-operation was impaired.

Benzodiazepines are used frequently as premedicants before general anaesthesia because of their anxiolytic, sedative and hypnotic properties. In addition, their anticonvulsive and muscle-relaxing properties can be used to advantage in association with regional anaesthesia. Midazolam, a water-soluble benzodiazepine, has central nervous effects similar to those of diazepam (Pieri, Scheffner and Scherschlicht (1981). Following injection i.v. it is twice as potent as diazepam, and its action is of shorter duration (Dundee et al., 1980); following injection i.m., it is better absorbed and causes less local irritation (Crevoisier et al., 1981). The present study was undertaken to assess the potential advantages of midazolam 0.1 mg kg^{-1} i.m., and to compare these with those of diazepam 0.2 mg kg^{-1} i.m. and placebo when used as medication before regional anaesthesia.

PATIENTS AND METHODS

Seventy-six male patients undergoing urological procedures under spinal anaesthesia were studied. The study was approved by the local ethics committee and informed written consent was obtained from each patient. Patients receiving sedatives, neuroleptic drugs and barbiturates were excluded from the study, and the patients included in the study had not been given any other premedicant for at least 72 h before the definitive operation. Midazolam 0.1 mg kg^{-1}, diazepam 0.2 mg kg^{-1} or 0.9% sodium chloride 2 ml was injected in a double-blind randomized manner to the vastus lateralis muscle before the patient was taken to the induction room. The time between premedication and the first assessment of the effects of the premedicant (by the anaesthetist, on the arrival of the patient in the induction room) was between 5 and 10 min. Subjective and objective assessments were obtained at this time and every 30 min for up to 2 h as described by Dundee, Moore and Nicholl (1962). In addition, the amnesic actions of the drugs were assessed, and heart rate, respiratory rate and systemic arterial pressure measured over this period. The patients were asked about pain on injection and the injection site examined for signs of inflammation or persisting pain at 72 h following surgery.

The individual points of each assessment were scored in respect to side effects and desired effects, and a net score was calculated. Sedation, apprehension and excitement, comprising the "efficacy

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score", were judged and classified as follows: patient awake = 1, moderately drowsy = 2, asleep but responsive = 5, asleep but non-responsive = 3; no apprehension = 0, moderate apprehension = –0.5, marked apprehension = –1; no excitement = 0, moderate excitement = –0.5, marked excitement = –1. For the "toxicity score", the following undesired effects were looked for: pain at or after injection, dizziness and nausea. If there were no toxic effects, 1 was subtracted in calculating the "net score". If there were toxic effects, –2 plus –1 for each toxic effect was added to the efficacy score to form the net score. Thus, the best possible efficacy score was 4; the best net score was 4 and the worst net score –5.

All subjective and objective assessments as well as the provision of regional anaesthesia were undertaken by the same anaesthetist. Statistical analysis of the results was with the chi-square test.

RESULTS

The groups did not differ significantly with regard to age, weight, ASA classification, or duration of surgery (table I). Operations included transurethral resection of the prostate, operations on the bladder and suprapubic prostatectomy.

TABLE I. *Details of patients receiving midazolam 0.1 mg kg^{-1}, diazepam 0.2 mg kg^{-1} or placebo (0 9% sodium chloride 2ml)*

	Age (yr) (Mean ± SD)	Weight (kg) (Mean ± SD)	Physical status		Duration of operation (min) (Mean ± SD)
			2	3	
Midazolam (*n* = 27)	67.6 ± 5 9	74.7 ± 11.7	18	9	45 ± 13
Diazepam (*n* = 25)	67.7 ± 6.4	72.8 ± 9.5	16	9	49 ± 12
Placebo (*n* = 23)	69.5 ± 5.6	71.0 ± 8.5	18	8	43.5 ± 10

Hypnotic properties. There was a striking difference between the sleep-inducing effects of midazolam and diazepam in the doses used (table II). Only one of the patients receiving diazepam went to sleep—after 90 min in the operation theatre. The maximum sedative effect of diazepam was apparent between 90 and 120 min. In the midazolam group, three of 27 patients were already asleep on arrival in the induction room; 30 min later, 13 patients were asleep and by 60 min 20 patients were asleep. By 90 min, 16 of the patients receiving midazolam were still lightly asleep, and although by 120 min only five remained asleep, all could be awakened easily. In three of the patients premedicated with midazolam 0.1 mg kg^{-1}, the depth of sleep at 30 min was such that co-operation was impaired.

Anxiety. Differences similar to those noted above were evident for the rapidity of onset and the potency of the anxiolytic effects between the two drugs (table II). After 60 min, and up to the end of the period of observation, none of the midazolam-premedicated patients was judged to be anxious. The maximum anxiolytic effect under diazepam was seen between 90 and 120 min, only two of the 25 patients in this group being apprehensive at this time.

Amnesia. Twenty-two of the patients in the midazolam group had total anterograde amnesia from the time they arrived in the induction room until the end of the procedure. Three were partially amnesic regarding either the operative intervention or the application of spinal anaesthesia. There was no evidence of amnesia in the other two groups.

Local pain. There were two patients in the diazepam group, one in the placebo group, and none in the midazolam group who reported pain on injection. No signs of inflammation, or of pain on compression, were evident 72 h later, in any patient in any group.

Undesirable side effects. One patient (diazepam) complained of slight dizziness at the beginning of the investigation, and one patient (placebo) after 120 min (in the recovery room). One patient in each group complained of moderate headache 24 h following operation. No serious cardiovascular or respiratory complications were observed. During the period of observation, decreases in arterial pressure of more than 20 mm Hg below the value

TABLE II. *Assessment of the desired effects from the time of arrival in the induction room until 120 min later. Figures represent percentage of effects in either group. M = midazolam 0.1 mg kg^{-1}; D = diazepam 0.2 mg kg^{-1}, P = placebo (0.9% sodium chloride 2 ml)*

	% Incidence with the three different premedicants in respect to time														
	Arrival in induction room			30 min			60 min			90 min			120 min		
Desired effects	M	D	P	M	D	P	M	D	P	M	D	P	M	D	P
Sleep induction:															
Awake	52	96	97	11	88	94	4	64	91	15	68	96	22	68	96
Sleepy, tired	37	4	3	41	12	6	22	36	9	26	28	4	59	32	4
Asleep responsive	11	0	0	37	0	0	59	0	0	59	4	0	19	0	0
Sleepy non-responsive	0	0	0	11	0	0	15	0	0	0	0	0	0	0	0
Apprehension:															
Absent	63	40	25	93	48	50	100	68	79	100	92	88	100	92	88
Moderate	30	26	50	7	40	34	0	28	9	0	4	12	0	4	12
Marked	7	24	25	0	12	16	0	4	12	0	4	0	0	4	0
Excitement:															
Nil	52	32	34	74	48	42	96	76	66	89	92	79	92	92	79
Slight	33	48	38	26	36	33	4	16	25	7	4	21	4	4	17
Marked	15	20	28	0	16	25	0	8	9	4	4	0	4	4	4

measured on arrival in the induction room were noted in four patients in each of the two groups receiving premedication. In the placebo group, this was the case with one patient only. Differences between systolic arterial pressures measured the day before the operation and after arrival in the induction room were seen only in the midazolam-premedicated patients (table III), arterial pressure being on average 11% lower than on the previous day (both measurements were obtained by the same anaesthetist).

The airway was well maintained without assistance in all patients.

Scores. Statistically, the net score and the efficacy score were significantly better over the whole period during which they were assessed for midazolam compared with both placebo and diazepam (table IV). It was only after 90 min that the net score for diazepam was better than that for the placebo. There were no significant differences between the three groups regarding the toxicity scores.

TABLE III. *Average systolic arterial pressures (mm Hg) (mean ± SD) of the day before operation and after arrival in the induction room*

	Day before op. (mm Hg) (mean ± SD)	Arrival in induction room (mm Hg) (mean ± SD)	Δ %
Midazolam 0.1 mg kg^{-1}	148.1 ± 12	131.7 ± 10	11
Diazepam 0.2 mg kg^{-1}	140.4 ± 9	140.2 ± 13	0.1
Placebo 0.9% NaCl 2 ml	145 ± 14	142.9 ± 12	1.4

Subjective assessment (patients). Differences between the midazolam, diazepam and placebo groups were also evident in the patients' subjective classification of sedative properties (table V). Twenty-one of the 27 midazolam patients classified the sedation as very good, whereas only one of the patients in the diazepam group and no patient in the placebo group did so. Differences were also noted between the amnesic effects of midazolam and diazepam (table VI).

In contrast to patients receiving diazepam or placebo, only one patient in the midazolam group judged the venous puncture, the application of the spinal anaesthesia, or the operation as unpleasant. Only placebo patients classified at least one of the procedures as very unpleasant. Most patients in all groups were content with this type of anaesthesia for their operation: all patients would again choose spinal anaesthesia for a similar intervention. Two patients who were studied twice were disappointed with their second premedication, which was diazepam in one and placebo in the other, after

TABLE IV. *Average scores of the three groups at the different times of assessment. M = midazolam 0.1 mg kg^{-1}, D = diazepam 0.2 mg kg^{-1}; P = placebo (0.9% sodium chloride 2ml).* P = *value of probability (χ^2 test). *No statistically significant difference between the toxic scores of the three groups.* *P *<0.005;* ***P *<0.001*

	Arrival in induction room			30 min			60 min			90 min			120 min		
Average scores	M	D	P	M	D	P	M	D	P	M	D	P	M	D	P
Efficacy score	0.65	–0.9	–0 98	2.35	–0.42	–0.63	3.09	0.38	–0.22	2.81	0.6	–0.09	1.94	0.52	–0.15
P v. midazolam	—	*	*	—	***	***	—	***	***	—	***	***	—	*	***
P v diazepam	*	—	ns	***	—	ns	***	—	ns	***	—	*	*	—	ns
Toxic score	0	–0.12	–0.08	0	0	–0.04	0	0	0	0	0	0	0	0	–0.04
Net score	0.65	–1.02	–1 06	2.35	–0.42	–0.67	3.09	0.38	–0.22	2.8	0.6	–0.09	1.94	0.52	–0.19
P v midazolam	—	*	*	—	***	***	—	***	***	—	***	***	—	*	***
P v diazepam	*	—	ns	***	—	ns	***	—	ns	***	—	*	*	—	ns

TABLE V. *Subjective classification of the sedative properties of the three different premedicants, by the patients*

	Percentage of patients in the different groups		
Degree of sedation	Midazolam 0 1 mg kg^{-1}	Diazepam 0.2 mg kg^{-1}	Placebo 0.9% NaCl 2 ml
Very good	81	4	0
Good	15	20	0
Sufficient	0	40	65
Insufficient	4	36	35

TABLE VI. *Patients' recall of procedures and classification of the degree of inconvenience. M = midazolam 0.1 mg kg^{-1}; D = diazepam 0.2 mg kg^{-1}; P = placebo (0.9% NaCl 2 ml)*

	Percentage of patients in the different groups								
Degree of	Venous puncture			Application of spinal anaesthesia			Operation		
inconvenience	M	D	P	M	D	P	M	D	P
No recall	85	0	0	85	0	0	81	0	0
Not unpleasant	11	84	92	11	92	83	19	88	96
Unpleasant	4	16	4	4	8	13	0	12	0
Very unpleasant	0	0	4	0	0	4	0	0	4

having had midazolam on the previous occasion.

DISCUSSION

The purpose of the study was to investigate the sleep-inducing, sedative and anxiolytic effects of midazolam and diazepam i.m. and to compare these with the effects of a placebo. In a previous study in which we compared the respiratory depressant effects of midazolam 0.1 and 0.15 mg kg^{-1} i.m. during regional anaesthesia (Reinhart et al., 1983), respiratory depression was found to be more pronounced in the higher-dose group, and the depth of sleep achieved to be too deep in some patients. Thus, in the present study a dose of midazolam 0.1 mg kg^{-1} was used.

The results show that midazolam i.m. was a potent hypnotic and anxiolytic agent in the dose used, although in four of the patients (mean age 67.6 ± 5.9 yr), even this lower dose must be judged as being too high, since co-operation with these patients was difficult. Possibly, the dose should be reduced further in the very old, or in debilitated patients.

The rapid onset of action after only 10 min, the maximum effect after 60 min, and the rapidity of recovery (after 90 min) are consistent with the results of Crevoisier and colleagues (1981) and Grote and colleagues (1980) on the relation between plasma concentrations of midazolam, after i.m. administration, with psychometric tests as well as with sleep EEG. In a study of our own, we found the highest midazolam concentrations in the cerebrospinal fluid 40–60 min after administration i.m. (Heinemeyer et al., 1982). Additionally, the most prominent respiratory effects were observed at this time. Midazolam i.m. is absorbed much more rapidly than diazepam; thus, although the dose of diazepam was twice that of midazolam, the onset of action of the former was later and the effect achieved much less pronounced. In comparing diazepam and midazolam i.v., Dundee and co-workers (1980) found midazolam to be about twice as potent (weight for weight) as diazepam. According to our results, this is not so following *intramuscular* injection when diazepam is dissolved in propylene glycol. Obviously diazepam, being relatively lipid-soluble and water-insoluble, is not absorbed as rapidly as the water-soluble benzodiazepine (Greenblatt and Shader, 1974).

The time course of action of midazolam, together with the effects observed in this and other studies make it very useful as a premedicant before regional anaesthesia, because the drug has already started to act before the spinal anaesthetic is administered, and has its maximum effect while the patient is in the operating theatre. In the recovery room, most of the patients were awake or only lightly asleep. The amnesia for the procedures in the operating theatre, often feared by patients under regional anesthesia, was appreciated especially by the patients.

Diazepam had almost no amnesic or hypnotic activities until near the end of the operation, and these then persisted in the recovery room. The observed lack of amnesia is in accord with Pandit and Dundee (1970), who found no significant anterograde amnesia with diazepam i.m. The known hangover effects of diazepam are attributable to its long half-life with enterohepatic recirculation and active metabolites (Klotz, Antonin and Bieck, 1976) and make diazepam i.m. unsuitable as premedication in this dosage. The lack of efficacy of diazepam in the first 60 min, the most stressing time for the patient, can be seen from its similarity to placebo at this time. Only after this time did the efficacy and the net scores for diazepam become significantly better than placebo.

Neither diazepam nor midazolam produced any significant side effects. There were no differences in toxicity score compared with patients receiving placebo only. Unlike Grote and co-workers (1980), studying human volunteers, we had no patient with difficulty maintaining the airway. Nevertheless, patients should be supervised by experienced medical personnel until more experience has been gained as to the degree of respiratory depression (Forster et al., 1980). In a previous study (Reinhart et al., 1983), we noted increases in arterial carbon dioxide tension, and decreases in arterial oxygen tension similar to those that can occur during natural sleep.

In conclusion, midazolam appears to offer the following advantages: rapid onset of action, greater sedative and anxiolytic effects, anterograde amnesia, and a rapid termination of activity. Midazolam would appear to be unsuitable as a premedicant if administered considerably more than 1 h before the anticipated procedure. In this particular situation, diazepam might offer advantages when given orally, or in a preparation that improves absorption following i.m. administration.

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PREMEDICATION BEFORE DAY SURGERY

A Double-Blind Comparison of Diazepam and Placebo

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SUMMARY

Premedication with diazepam 0.25 mg kg^{-1} by mouth was compared with placebo in a double-blind trial in patients undergoing day-case surgery under general anaesthesia. Diazepam decreased significantly preoperative discomfort and apprehension. The patients were discharged on time regardless of the type of premedication, and complaints at the time of discharge and on the following day could be related only to the length of anaesthesia and not to the type of premedication. Premedication given early in the morning remained effective for up to 6 h.

The benzodiazepines are used widely as premedication in patients before surgery (Kangas, Kanto and Mansikka, 1977; Korttila et al., 1978; Kanto, Kangas and Mansikka, 1979; Studd and Eltringham, 1980). The absorption of orally administered diazepam is rapid and its duration of action relatively long. Indeed, premedication with diazepam may have certain advantages over premedication with chlordiazepoxide, morphine, promethazine and placebo. In particular, its sedative effects, when weighed against the side-effects, were better than those of the other agents (Haslett and Dundee, 1968) and an anxiolytic effect, without concurrent troublesome drowsiness, has been documented (Dundee and Haslett, 1970).

At Frederiksborg County Hospital, Hørsholm, Denmark, approximately 40% of the elective surgery is performed on an outpatient basis. Thus, it is important that any drugs given to patients undergoing such surgery do not influence the patient's condition after surgery. The present investigation examined the need for premedication before outpatient surgery and its influence on the general condition of the patient after surgery.

PATIENTS AND METHODS

The study was conducted as a double-blind, randomized investigation in which diazepam (tablets: Apozepam, AL-pharma, Copenhagen) 0.25 mg kg^{-1} was compared with placebo.

Patients admitted to the day-unit for minor surgical procedures such as hernia repair, treatment of varicose veins, excision of benign breast tumours, dilatation and curettage (D and C), laparoscopic sterilization, endoscopy and minor orthopaedic operations were studied.

Before admission a physical examination was performed and informed consent obtained. Each patient fulfilled the following criteria for inclusion in the study:

(1) Age 15–60 yr
(2) Weight > 40 kg
(3) No concurrent psychoactive drug therapy
(4) No abuse of alcohol
(5) Healthy apart from the condition requiring surgical intervention

Only patients receiving general anaesthesia were included. Premedication was given at 08.00 h on the day of the operation, regardless of the time of surgery. Operations were, as far as possible, completed during the morning so that the patient could be discharged the same evening.

One of three techniques of anaesthesia was used:

(1) Induction: Thiopentone i.v.
Maintenance: Oxygen–nitrous oxide inhalation,

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possibly supplemented by thiopentone i.v.

(2) Induction: Thiopentone i.v.
Maintenance: Oxygen–nitrous oxide–halothane by inhalation.

(3) Induction: Thiopentone i.v.
Maintenance: Oxygen–nitrous oxide–halothane by inhalation plus myoneural blockade.

In some patients, atropine and fentanyl were given i.v. if deemed necessary.

Data were collated on two forms: one was filled in by the anaesthetist immediately before induction of anaesthesia and contained the following questions:

(a) "Does the patient present any of the following symptoms: Paleness, perspiration, cold extremities, dry mouth, slurred speech, emesis or vomiting?"

Each question to be answered with a "yes" or a "no".

(b) "Is the patient in a satisfactorily non-apprehensive state?"

On the basis of the answers to question (a), question (b) was answered. Only lack of all the first four symptoms mentioned, was recorded as a non-apprehensive state.

The same evening, an estimate of the patient's general condition was obtained. To be considered fit for discharge, the patient had to fulfil the following criteria:

(1) Fully awake.
(2) In the upright position without discomfort.
(3) Willing to go home.
(4) Under observation by a responsible adult during the night at home.
(5) Transported home by a second person.

The estimate of the patient's general condition was made as follows:

(c) 1. Patient unaffected by anaesthesia, discharge recommended.
2. Patient slightly affected by anaesthesia, discharge recommended.
3. Patient very affected by anaesthesia, discharge not recommended.

At the time of discharge a second form (table I) was given to the patient, who was asked not to read the questions until the following day.

The chi-square test was used for the statistical evaluation; the level for a significant difference was taken as $P = 0.05$.

RESULTS

The study comprised 202 patients: 104 (85 women) were premedicated with diazepam and 98 (82 women) received placebo.

TABLE I. *Discharge questionnaire*

(a) "Did you have any alcohol, wine or beer on the evening before the operation? If 'yes ', please specify "

(b) "Did you have any tranquilizer or hypnotic on the evening before the operation? If 'yes', please specify "

(c) "Did you experience the stay in the ward, before the operation, but after you had your premedication as
1 unpleasant?
2. not unpleasant?
3. do not remember?"

(d) "Did you experience the stay in the operating room as
1. unpleasant?
2 not unpleasant?
3. do not remember?"

(e) "In case of any discomfort experienced, did this discomfort consist of
1. nausea?
2. vomiting?
3. headache?
4. dizziness?
5 palpitations?
6. tiredness?
7. apprehension?
8 excitement?"

(f) "Did you experience any discomfort while waking up from the anaesthesia?"

(g) "At *the time of discharge,* did you experience any discomfort like
1. drowsiness?
2. tiredness?
3. headache?
4. nausea?
5. vomiting?
6. dizziness?
7. reduced power of concentration?"

(h) "*The day after the operation,* did you experience any of the following symptoms:
1. drowsiness?
2 tiredness?
3. headache?
4. nausea?
5 vomiting?
6. dizziness?
7. reduced power of concentration?"

The randomization was tested by means of the Mann–Whitney rank sum test and was found to be satisfactory. The two test groups were comparable with regard to age, sex, weight, length of anaesthesia, type of anaesthesia and type of surgical intervention.

Observations before surgery on the day of operation

Diazepam was superior to placebo in that it decreased preoperative fear and anxiety. No sig-

TABLE II. *Numbers of patients experiencing preoperative discomfort*

Type of discomfort	Diazepam ($n=104$)	Placebo ($n=98$)	P
Anxiety	10	31	<0.005
Fear	3	10	<0.05
Tiredness	9	5	ns
Headache	3	8	ns
Dizziness	5	2	ns
Nausea	1	3	ns
Vomiting	0	0	ns
Difficulty concentrating	1	0	ns
Chills	0	2	ns
Dyspnoea/feeling of oppression	1	0	ns
Total number of patients experiencing discomfort	20	41	<0.0005

nificant difference in symptoms such as tiredness, headache, dizziness, nausea and vomiting was seen between the two groups (table II). One patient premedicated with diazepam complained of dyspnoea and a feeling of oppression. She had experienced similar symptoms previously, after taking diazepam. This was the only patient experiencing unforeseen effects from the medication. The operation was performed as planned, and the patient was discharged in a satisfactory condition.

The surgical procedures performed and the number of patients with preoperative discomfort related to type of operation are shown in table III.

TABLE III. *The number of patients undergoing the various surgical procedures (Number of patients claiming preoperative discomfort)*

Type of operation	Diazepam ($n=104(20)$)	Placebo ($n=98(41)$)
Abortion	38(8)	39(17)
Laparoscopic sterilization	15(5)	10(5)
Dilatation and curettage	11(3)	12(4)
Operation for varicose veins	11(1)	11(4)
Operation for inguinal hernia	11(1)	7
Minor orthopaedic surgery	7(1)	10(3)
Operation for mammary tumour	8(1)	3(2)
Others	3	6(6)

From the anaesthetist's evaluation of the degree of sedation before operation, those who had received diazepam were significantly less apprehensive. The combination "subjectively satisfied patient"/"objectively non-apprehensive patient" was found significantly more frequently in those who had received diazepam (table IV).

The preoperative waiting time was the same in both groups. Among those patients experiencing subjective discomfort and inadequate sedation, the number of patients who waited a short time, a medium period of time and a long time (maximum 6 h) did not deviate significantly from the expected.

Observations after surgery on the day of operation

The number of patients who experienced discomfort while waking up from anaesthesia did not differ significantly between the two groups. In particular, no increase in amnesia was recorded after diazepam. The patients experiencing discomfort could not be characterized with regard to type of operation performed, or the technique or duration of anaesthesia.

The number of patients discharged "objectively unaffected, on time" did not differ significantly when the two groups were compared and the duration of anaesthesia was taken into account. A significant increase in the number of patients who were discharged "slightly affected, on time" was found among those who had been anaesthetized for more than 45 min (fig. 1).

Only two patients were not discharged on time. One patient in the diazepam group who had undergone laparoscopic sterilization had to be transferred to the ward because of pain and vomiting. One patient in the placebo group could not be discharged because of pain after an operation for epicondylitis lateralis humeri.

At the time of discharge, the number of patients with complaints was not significantly different in the two groups. Based on the patient's own evaluation, no relationship between duration of anaesthesia and discomfort experienced could be shown (fig. 2).

The day after operation

There was no significant difference between the

TABLE IV. *Evaluation of the degree of sedation before surgery*

	Diazepam ($n=104$)	Placebo ($n=98$)	P
Anaesthetist's evaluation			
Number of non-apprehensive patients	83	55	<0.005
Combined evaluation by the patient and the anaesthetist			
Both satisfied	71	37	<0.0005
Both dissatisfied	8	23	<0.005
One satisfied, one dissatisfied	25	38	<0.05

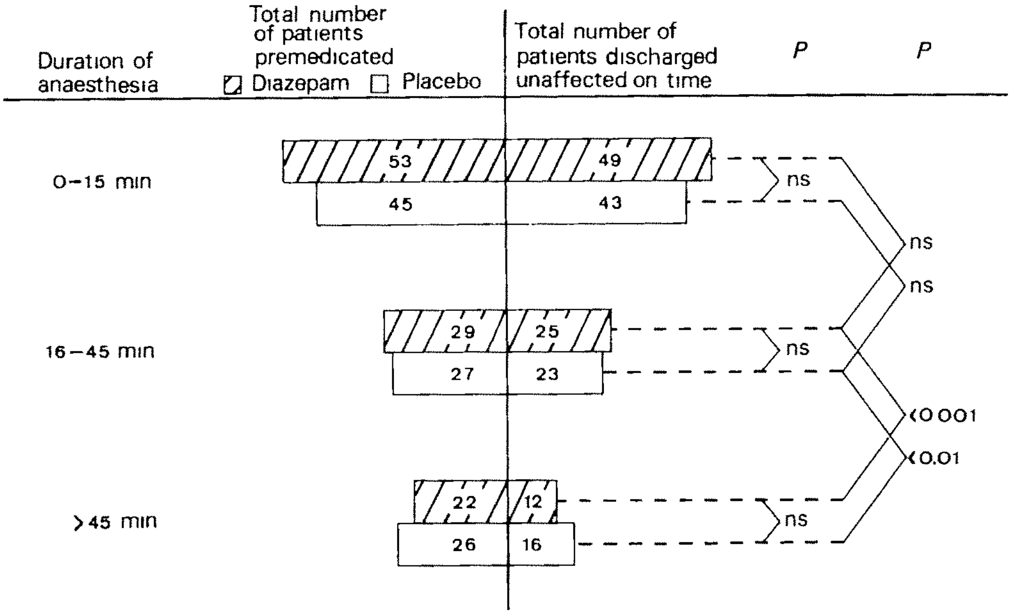

FIG 1 Number of patients discharged *objectively* unaffected, on time

patients treated with diazepam or placebo (fig. 3).

All patients anaesthetized for less than 15 min received anaesthetic technique 1, while those anaesthetized for longer than 15 min received anaesthetic techniques 2 or 3.

In the diazepam and the placebo groups, 67 and 69 of the patients, respectively, received fentanyl 0.05–0.15 mg during anaesthesia. No difference in fentanyl dosage between subgroups (e.g. short or long anaesthesia) or relationship between fentanyl

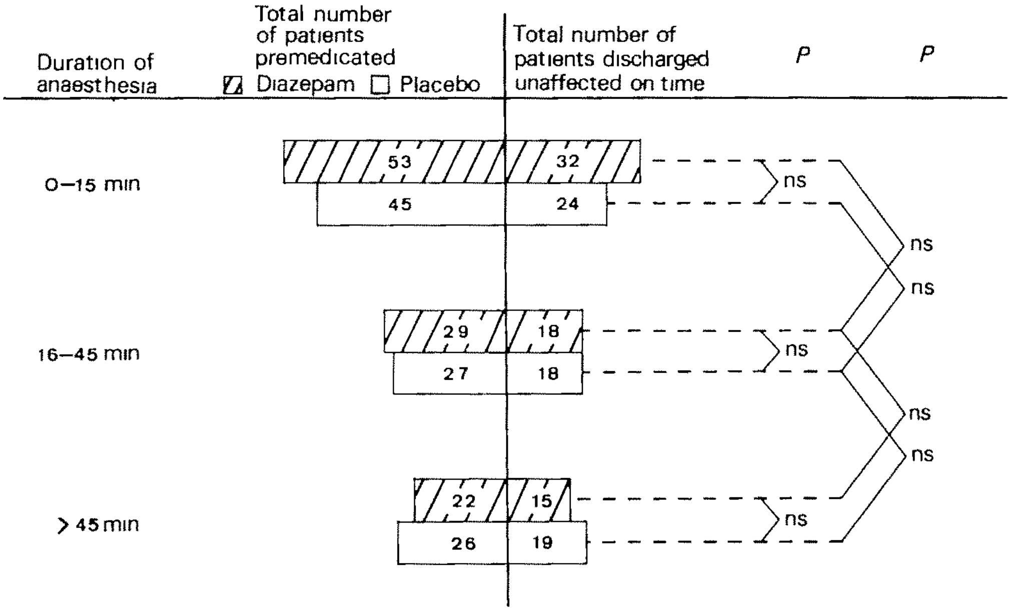

FIG 2 Number of patients discharged *subjectively* unaffected, on time.

TABLE I. *Angles of retroflexion of the head (mean (SD)) in 20 patients. Significance calculated with the* t *test for paired values: conditions compared with the "no-adjunct" group* — †$P < 0.001$; *elevations of 0 and 8 cm compared with the values measured at 4 cm* — **$P < 0.01$; ***$P < 0.001$

	Upper airway closed	Upper airway clear		
Elevation of occiput	Neutral position	No adjunct	Oral airway	Nasal airway
0 cm	105 (9.1) † ***	114 (7.1) **	114 (5.5) ns **	112 (6.8) ns ***
4 cm	96 (6.5) †	109 (5.5)	110 (5 5) ns	106 (7.1) ns
8 cm	91 (2.3) † **	102 (8.2) ***	101 (9.3) ns ***	97 (10.8) † ***

observed that it was possible to obtain an airtight seal in the upper airway with the epiglottis alone.

The hyoid bone is horse-shoe shaped and can be moved in all directions by the action of the extrinsic pharyngeal muscles, although there is some restriction to movement in a caudal direction. The thyroid cartilage is suspended from the hyoid bone and it is fixed dorsally to the dorsal conjoined tendon of the pharyngeal muscles, which is in turn connected to the prevertebral fascia.

The epiglottis hangs, like the lid of a bin, from the posterior aspect of the hyoid with the thyro–epiglottic ligament acting as the hinge and the hyo–epiglottic ligament acting as the lever for the lid. In the cadaveric preparations it was demonstrated that the position of the epiglottis in the hypopharynx depended principally on the relative position of the hyoid in relation to the thyroid cartilage.

Patients

The angle of retroflexion (table I) necessary to open the airway was not altered substantially by the use of artificial airways in the hypopharynx. However, in eight of the 20 patients, with a naso–pharyngeal airway at 8 cm elevation, and in one patient at 4 cm elevation, there was a small difference in the required angle of retroflexion compared with the angle in the neutral position. In these patients the nasal airway supported the epiglottis clear of the retropharyngeal wall. In the other patients the angle of retroflexion required to open the airway was significantly greater than that present in the neutral position. The angle of retroflexion, required to achieve a clear airway became smaller as the occiput was elevated, and once the airway began to open, only a little more tilt was required to open it fully (fig. 2).

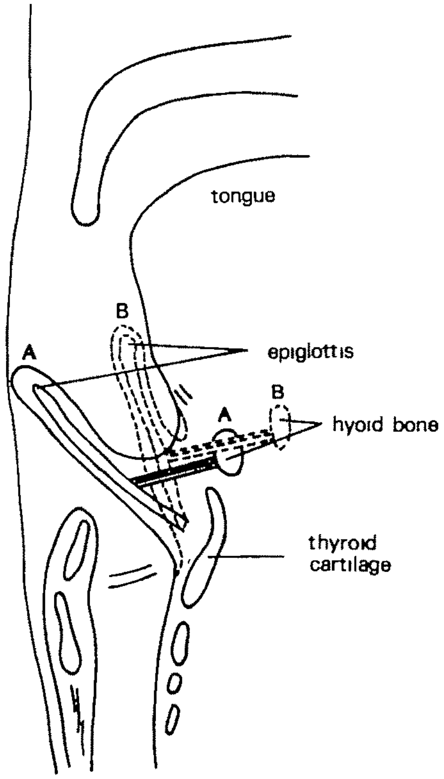

FIG. 2. Cross-section of the larynx, showing obstruction of the upper airway by the epiglottis (A). Anterior displacement of the hyoid bone by the extra pharyngeal muscles clears the airway (B).

The *mechanism* of airway closure was visualized using the flexible bronchoscope. With this method it could be demonstrated that the epiglottis was sucked over the entrance to the trachea by the inspiratory pressure and this occurred well before the tongue even approached the posterior pharyngeal wall. The airway was closed as the rims of the epiglottis reached the pharyngeal wall. When attempts were made to ventilate a patient with the epiglottis in this position, the pars glottica could be seen being forced into the oesophagus. The gas mixture might then enter the oesophagus and be passed into the stomach. As the head was extended the epiglottis was withdrawn from the tracheal entrance. When partial obstruction occurred and the top of the epiglottis vibrated in the lower pharynx, the characteristic snoring sound could be heard.

DISCUSSION

These observations indicate that the tongue is not the only factor concerned with upper airway obstruction. The mechanism is more complicated and it seems necessary to reconsider the facts. The data presented by Safar and colleagues (1959) were accurate, but their conclusion, that the tongue is the sole source of upper airway obstruction, is not wholly justified, as it has been shown that the airway may close even when the tongue is bypassed.

The hyoid bone can be considered as forming the boundary of the wide end of two funnels, the larynx and the pharynx, both of which are suspended from the base of the skull and extend into the thorax. Which funnel is opened/closed is determined by the position of the epiglottis which, in turn, depends on the antero-posterior position of the hyoid bone in relation to the thyroid cartilage. This position may be altered voluntarily by the extrapharyngeal musculature of the hyoid bone, whereas the thyroid cartilage remains rather immobile. It seems that the omohyoid muscle, and the anterior belly of the digastric muscle, are essential to manoeuvre the hyoid bone towards its ventral position. It is obvious that this does not occur in unconscious patients. For the same reason, it is probable that the triple airway manoeuvre (Morikawa, Safar and DeCarlo, 1961) remains the most successful method of opening the airway because this manoeuvre moves the hyoid ventrally. On the other hand, the introduction of a stomach tube and an oesophageal obturator airway should be assisted by flexion of the neck, to push the hyoid bone backwards.

This investigation showed that the airway is

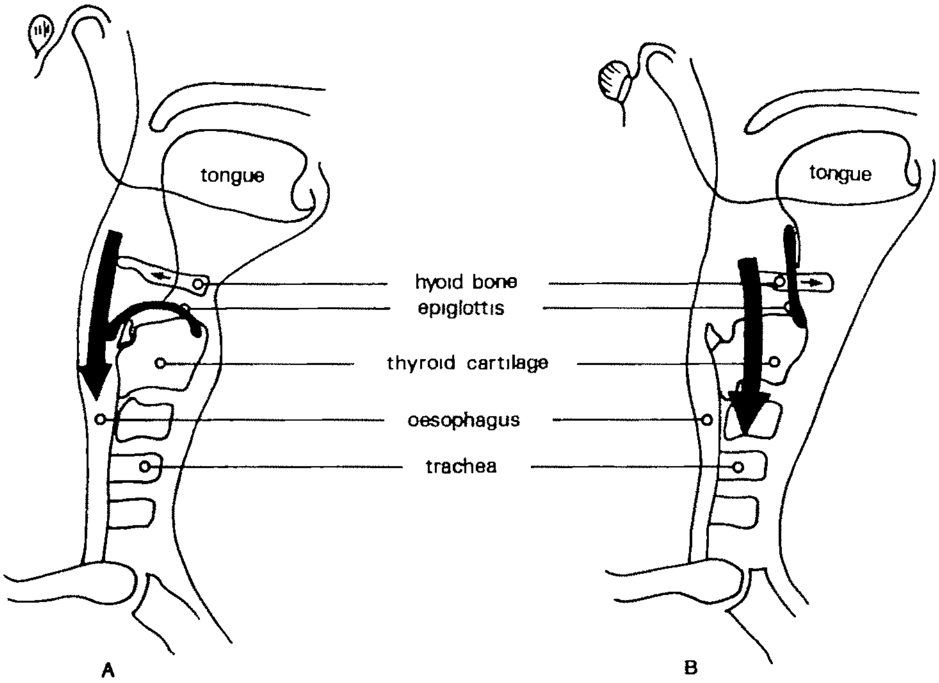

FIG. 3. The position of the hyoid bone determines which of two funnels is opened/closed. Note that the tongue is pushed away by the pressure of the epiglottis in position (B).

almost invariably closed when the head is in its neutral position, and that the use of artificial airways did not always guarantee a clear airway. The airway was clear when the nose or the mouth, or both were open, and the epiglottis did not reach to the posterior pharyngeal wall. The tongue may obstruct the upper airway in two ways. It may push the soft palate against the posterior pharyngeal wall, obstructing both the nasal and oral cavities. The tongue may close the oral cavity when the nose is obstructed, then acting as a one-way valve obstructing expiration. In both cases of obstruction by the tongue there is an indication for Mayo or Guedel type airways. Obstructions of this type were not seen during this study, but are occasionally noticed in patients with a dental prosthesis. The effect of opening the mouth with a Mayo airway does not decrease significantly the angle of retroflexion, nor does the introduction of artificial airways. Only the elevation of the head decreases the head tilt necessary to clear the airway. When the head is elevated, a nasal pharyngeal airway of sufficient length to support the epiglottis will often provide a clear airway and decrease the angle of retroflexion significantly. However, in these patients it was possible to obstruct the upper airway by flexion of the neck.

This concept of airway closure may contribute to the training of medical and paramedical personnel and explain the management of the airway and the use of artificial airways, stomach tubes and tracheal tubes. However, at present it does not seem prudent to give such complicated detailed information during the training of the lay public, although it may be possible to use a simplified version of this concept.

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THE VENTILATORY RESPONSE TO CARBON DIOXIDE

An Analysis of Data Obtained by the Rebreathing Method

N. W. GOODMAN AND J. S. H. CURNOW

SUMMARY

The ventilatory response to carbon dioxide using the rebreathing method was studied repeatedly in four healthy volunteers. The data were collected and processed in different ways using a microcomputer. Least squares linear regression analysis described the responses almost as accurately as a non-linear second-order polynomial regression. Linear regression analysis was undertaken on $\dot{V}_I/P_{E'_{CO_2}}$ points, first breath-by-breath and then on three different groupings of breaths. The gradients and intercepts obtained by grouping agreed with those from breath-by-breath analysis both for a single response and for the mean result of a number of responses. Grouping tended to increase the correlation coefficient of a response, but widened the statistical confidence limits of the calculated gradient. The performance variability between repeated responses, the same no matter which data points were used, produced a range of gradients for each subject which was larger than the confidence limits on the gradient of a single response.

Since Read's method of estimating the ventilatory response to carbon dioxide by rebreathing (Read, 1967) is so much easier than the steady-state method, it has become a routine research procedure and a simple and instructive description of equipment, technique and analysis is available (Rebuck, 1976). A full response can be obtained in 3–4 min, although, generally, it takes longer to work out and plot the result. An *X–Y* plotter (Milledge, Minty and Duncalf, 1974; Jordan, 1981) can be used to plot the results quickly, but is sensitive to tuning, is not very versatile, and the actual values of the end-tidal carbon dioxide ($P_{E'_{CO_2}}$) and ventilation are not retained for statistical analysis.

Read's (1967) method of data analysis was to take successive 30-s intervals over the 4 min of rebreathing and construct each graph from seven or eight points representing the means of the calculated ventilation and $P_{E'_{CO_2}}$ for each interval. This is still the usual method of analysis and is recommended by Jordan (1982); Rebuck (1976) simplified it slightly by taking $P_{E'_{CO_2}}$ at the mid-point of each interval. Other methods have included taking successive 20-s intervals (Engineer and Jennett, 1972), the first four or five breaths in successive 30-s periods, groups of three consecutive breaths (Knill and Gelb, 1978), or just three points during the response and averaging over periods of approximately 30 s (Jennett, 1968). However, none of these authors gave any reason as to why they had chosen a particular method of analysis, nor claimed that their analysis, *per se*, improved the accuracy of the result. Strachova and Plum (1973) advocated estimating the minute ventilation and $P_{E'_{CO_2}}$ from *every breath*. However, unless the data could be collected and analysed automatically there would have to be a significant advantage in breath-by-breath analysis to justify the increase in time spent measuring off the record. Strachova and Plum claimed that there was such an advantage since this technique of analysis decreased the within-subject variability (Read, 1967; Sahn et al., 1977).

The microcomputer has made this method of analysis more accessible (Howie and Kenny, 1982). We have programmed a Nascom 2 to collect and store data on-line during tests of the ventilatory response to carbon dioxide, and have used the stored

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data to investigate alternative methods of analysis.

SUBJECTS AND METHODS

Subjects

Four healthy volunteers were studied. They were aged 30–32 yr and were conversant with respiratory physiology. Each subject performed 10 rebreathing tests in 3 days over the course of a month: two tests were invalid; 38 were analysed.

Respiratory equipment and technique

The equipment was similar to that described by Rebuck (1976) and is in frequent use by our group in clinical research (Malins, Goodman and Cooper, 1983). Subjects were fitted with a noseclip and breathed into and out of a 6-litre bag-in-box through a mouthpiece and low-resistance circuit. The bag was pre-filled with a 5–7% mixture of carbon dioxide in oxygen. Air-flow into and out of the box was measured with a Fleisch pneumotachograph head. The integrated flow signal (Gould–Godart) gave the inspired tidal volume which was calibrated with air from a 1-litre syringe (Super Syringe, Hamilton, USA). Carbon dioxide was measured continuously (Gould Capnograph), sampling from the circuit close to the mouth and returning the sampled gas to the expiratory limb of the circuit.

All responses were performed between 1130 and 1300 h. The subjects had been starved for at least 3 h and were sitting comfortably. The first 30–45 s of rebreathing, while the subject equilibrated with the carbon dioxide in the rebreathing bag, were ignored and the computer was instructed to start collecting data once $P\text{E}'_{\text{CO}_2}$ was seen to increase from the mixed venous value. This was verified more accurately from the paper record at the time of analysis. Each rebreathing manouevre lasted about 4 min.

The signals of inspired tidal volume and carbon dioxide were passed to a pen recorder (Gould 2400), and to 8-bit analogue-to-digital converters (bit equivalence: 0.047 kPa and 6.84 ml). The computer program was written in BASIC with subroutines in assembler when BASIC was too slow: it was essentially a peak-hold program that stored on disk the peaks of carbon dioxide and tidal volume, along with the corresponding respiratory period.

Routine analysis

For routine clinical research, the program collected the data and loaded a standard routine to analyse the response breath-by-breath by least squares linear regression, that is $\dot{V}\text{I} = a + (b \times P\text{E}'_{\text{CO}_2})$ (fig. 1). This is termed the 1–1B analysis. A graph was printed on the screen as well as the statistics: the gradient of the response (b: litre min^{-1} kPa^{-1}), the intercept of the line with the ventilation axis (a: litre min^{-1}), the intercept of the line with the carbon dioxide axis at zero ventilation, the ventilation at 7.3 kPa (55 mm Hg) calculated from the regression line, the correlation coefficient (r) and the value of t for the calculated gradient. Data could be edited out before analysis, for instance from breaths recorded before $P\text{E}'_{\text{CO}_2}$ was increasing at a constant rate (checked from the paper record), or from spurious breaths caused, for example, by swallowing. No data were erased from the disk.

Re-analysis

For the purposes of this study the responses were later re-analysed by a different set of routines.

For one subject (GC) the gradients calculated by conventional least squares regression were compared with the approximate functional linear relations estimated by Bartlett's technique (quoted by Davies and Goldsmith, 1976).

To test for significant non-linearity in the increase in ventilation with $P\text{E}'_{\text{CO}_2}$ or of $P\text{E}'_{\text{CO}_2}$ with time, the calculated breath-by-breath data were analysed by least squares regression to a second-order polynomial, for example for ventilation: $\dot{V}\text{I} = a + (b \times P\text{E}'_{\text{CO}_2}) + (c \times P\text{E}'_{\text{CO}_2})$, using a PDP-11 minicomputer. Whether the polynomial analysis gave a better fit was determined by applying an F test to the difference between the polynomial and linear regression sums of squares.

In addition to the regression statistics calculated by the routine analysis (see above), the extended analysis calculated also the standard error of the gradient of the carbon dioxide response and the confidence limits of the gradient (fig. 1). This analysis was achieved by taking: every breath (analysis 1–1B); consecutive groups of four breaths (analysis 4–4B); the first four breaths in each 30-s period (analysis 4–30S); and blocks that simply divided the whole response into three equal lengths (analysis N–N). These N–N blocks were usually about 20 breaths, that is, 1 minute or so, long.

RESULTS

Regression and the functional linear relation

For subject GC, the mean and the standard deviation of the 10 rebreathing manoeuvres were exactly the same by conventional least squares and Bartlett's method (Davies and Goldsmith, 1976). Bartlett's method was not used in the analysis of the responses of the other three subjects.

Analysing for non-linearity

On the paper record the increase in carbon dioxide with time appeared linear. The linear regression of the breath-by-breath $P\mathrm{E}'_{CO_2}$ with time gave correlation coefficients greater than 0.993 for all responses (mean 0.997). Despite this extremely close fit, the data were fitted better by a second-order polynomial in 25 of the 38 responses: 19 showed that the carbon dioxide was increasing more steeply with time as the response progressed, and six that it was increasing less steeply. However, the reduction in the residual sum of squares from a linear to a polynomial regression, although *statistically* significant, was small. For the worst case, when r was 0.993, polynomial regression decreased the residual standard deviation from 0.058 kPa to 0.021 kPa.

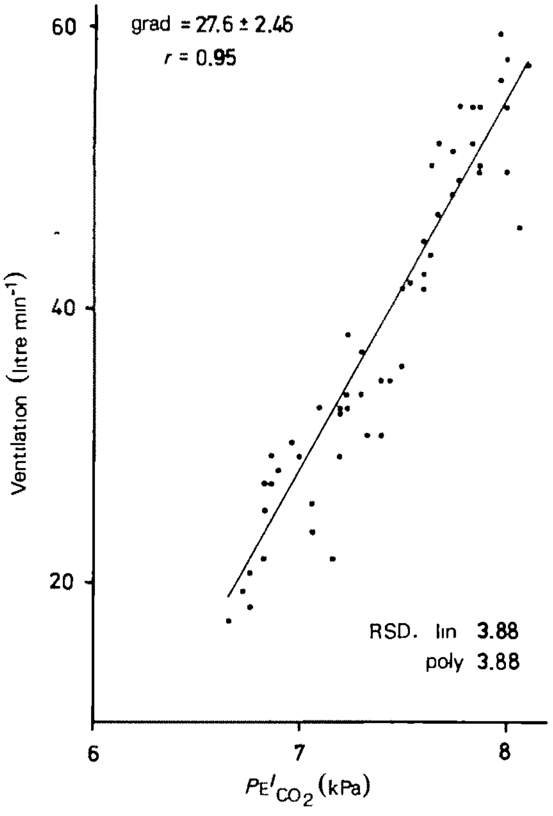

FIG 1. Breath-by-breath ventilation against end-tidal carbon dioxide during rebreathing (subject C.A.). Ventilatory response (gradient ±95% confidence limits on the gradient in litre $\mathrm{min}^{-1}\ \mathrm{kPa}^{-1}$) estimated by least squares linear regression ($y = 27.6x - 155\ 7$). Least squares polynomial regression did not alter the residual standard deviation (RSD)

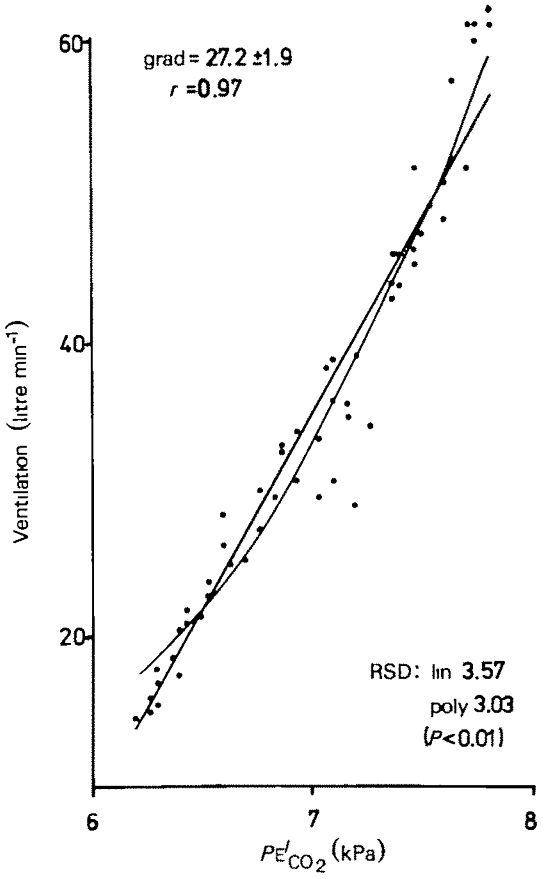

FIG 2. Breath-by-breath ventilation against end-tidal carbon dioxide during rebreathing (subject C.A.). Ventilatory response (gradient ±95% confidence limits on the gradient in litre $\mathrm{min}^{-1}\ \mathrm{kPa}^{-1}$) estimated by least squares linear regression ($y = 27.2x - 162\ 2$). Least squares polynomial regression ($y = -\ 102\ 4x + 1.23x^2 + 296$) significantly altered the residual standard deviation (RSD).

The polynomial fit to the data of ventilation against $P\mathrm{E}'_{CO_2}$ was, in statistical terms, significantly better than the linear fit in 23 of the 38 responses (table I). Because this analysis gave no easy indication of the direction of the non-linearity, each response was divided into halves containing equal numbers of breaths and the gradients for each half were determined by 1–1B analysis. Of the 23 responses that were fitted better by a polynomial, 19 steepened as the response progressed ($\chi^2 = 9.78$, df $= 1, P < 0.005$). In three of the four subjects the mean gradient of the second halves of the responses was steeper than that of the first half: in one subject (MS) the difference was significant at the 5% level. Subject GC had the most linear responses.

TABLE I. *Ventilatory responses to carbon dioxide in four healthy volunteers: a comparison of linear and polynomial least squares regression Left-hand columns: for each subject, the number of responses, the significance by* F *test of better fit by second-order polynomial, and the number of responses showing an increase or decrease of gradient in the second half of the response. Right-hand columns: means and standard deviations (SD) of the gradient (litre min^{-1} kPa^{-1}) of the first and second halves of the responses Analysis by least squares linear regression of ventilation and* $P_{E'CO_2}$ *from every breath.* P *is the probability of a chance occurrence of the observed difference between halves by paired* t *test*

	Is the polynomial a better fit?		Second half gradient up or down		Gradient of first and second halves of response (litre min^{-1} kPa^{-1})		
Subject	ns	$P < 0.05$				Mean	SD
C.A.	1	6	Up	– 7	1st	19.6	8.7
($n = 9$)	1	1	Down	– 2	2nd	27.4	7.7
						$P = 0.11$	
M S.	1	7	Up	– 8	1st	13.8	4.4
($n = 9$)	1	0	Down	– 1	2nd	21.4	4.8
						$P = 0.017$	
A.M.	2	4	Up	– 6	1st	16.7	5.8
($n = 10$)	3	1	Down	– 4	2nd	21.6	4.7
						$P = 0.075$	
G.C.	2	2	Up	– 4	1st	19.9	4.7
($n = 10$)	4	2	Down	– 6	2nd	18.3	4.4
						$P = 0.33$	
Totals	6	19	Up	– 25			
	9	4	Down	– 13			

Overall, even when there was a better fit by polynomial, the actual improvement over linear correlation was slight (fig. 2). The mean residual standard deviation for the 17 responses better fitted by a polynomial at $P < 0.01$ was decreased from 2.44 litre min^{-1} to 1.98 litre min^{-1}.

Analysing different groups of breaths

The grouping of data points made no significant difference to the estimates of gradient, the largest discrepancies from the 1–1B estimates being obtained with the 4–30S analysis. This was so for all subjects and is illustrated for subject CA in figure 3.

The confidence limits on each estimate of gradient represent the statistical variability which must be considered when looking at a single carbon dioxide response. The 4–4B confidence limits were each wider than those obtained by 1–1B analysis. The spread of the estimates is the within-subject, between manoeuvre, performance variability for the subject CA, and is compared with the confidence limits of each estimate in figure 3C.

Tables II and III summarize the results, as mean values, obtained from the four subjects by the four methods of analysis. Table II shows that the mean gradient for each subject, and the coefficient of variation about the mean (the within-subject variability), were largely unaffected by the method of analysis. On the other hand, in terms of mean values, the derived statistics (correlation coefficient, *r*, and the standard error, SE, and confidence limits, CL) attached to each estimate of the gradient *were* influenced by the method of analysis (table III).

Compared with the 1–1B method of analysis, the analyses on grouped points increased *r* and widened the confidence limits to an extent which paralleled the reduction in the degrees of freedom consequent on the grouping procedure. The intercepts of the carbon dioxide responses on the carbon dioxide axis were, like the gradients, little affected by the method of analysis—as shown by a comparison of the means obtained by 1–1B analysis and N–N analysis (table IV).

DISCUSSION

The validity of regression

We took conventional least squares regression as our standard technique because Bartlett's equation

TABLE II. *Means and the coefficient of variation (CV) between tests of the gradient (litre* min^{-1} kPa^{-1}*) of the ventilatory response to carbon dioxide in four healthy volunteers. Analysis by least squares linear regression taking different groupings of breaths for each graph point: every breath (1–1B); successive groups of four breaths (4–4B); four breaths from the beginning of successive 30-s periods (4–30S); blocks of breaths from each third of the response (N–N)*

	Subject							
	C.A. ($n = 9$)		M.S. ($n = 9$)		A.M. ($n = 10$)		G.C. ($n = 10$)	
Analysis	Mean	CV	Mean	CV	Mean	CV	Mean	CV
1–1B	23.9	18	16.8	9	18.9	19	19.8	19
4–4B	23.7	18	16.8	9	18.9	19	19.8	19
4–30S	23.1	21	15.9	14	18.6	23	20.5	22
N–N	23.8	19	16.9	10	18.9	20	19.7	19

TABLE III. *The mean correlation coefficient* (r), *mean standard error (SE) and mean confidence limits (CL)* (t × *SE) within tests of the gradients (litre* min^{-1} kPa^{-1}*) of the ventilatory response to carbon dioxide in four healthy volunteers. Analysis as in table II*

	Subject											
	C.A. ($n = 9$)			M.S. ($n = 9$)			A.M. ($n = 10$)			G.C. ($n = 10$)		
Analysis	r	SE	CL	r	SE	CL	r	SE	CL	r	SE	CL
1–1B	0.95	1.1	±2.1	0.96	0.7	±1.4	0.96	0.8	±1.5	0.98	0.6	±1.2
4–4B	0.97	1.7	±3.6	0.97	1.1	±2.5	0.98	1.1	±2.3	0.99	0.8	±1.7
4–30S	0.98	2.5	±5.9	0.98	1.7	±4.1	0.99	1.7	±3.8	0.99	1.1	±2.7
N–N	0.99	3.4	±42.9	0.99	1.8	±22.9	0.99	1.5	±19.1	1.0	1.4	±18.1

TABLE IV. *Means and the coefficient of variation (CV) between tests of the intercept (kPa) of the calculated ventilatory response to carbon dioxide with the carbon dioxide axis in four healthy volunteers. Analysis by least squares linear regression taking either every breath (1–1B) or blocks of breaths from each third of the response (N–N)*

	Subject							
	C.A.		M.S.		A.M.		G.C.	
Analysis	Mean	CV	Mean	CV	Mean	CV	Mean	CV
1–1B	5.89	5	5.53	3.5	5.76	2.4	5.16	6.9
N–N	5.87	5	5.49	4.7	5.73	3.3	5.16	7.0

for the approximate functional linear relation gave virtually the same result. This is discussed further in the following paper in this issue (Goodman and Black, 1985).

Non-linearity

We found that in many of the responses, a *statistically* significant non-linearity could be detected: ventilation tended to increase more steeply with PE'_{CO_2} as the PE'_{CO_2} increased. Nonetheless, the non-linearities were minor and linear regression analysis still gave an adequate description of the data points. Major non-linearities are to be expected if the initial FI_{CO_2} in the rebreathing bag is too low; typically there will be a dog-leg in the ventilatory response to carbon dioxide (Mustchin, 1977; Jordan, 1981). If measurement is started before equilibration, PE'_{CO_2} does not increase linearly with time and this will affect the initial part of the response. Others have noted minor non-linearities (Read, 1967), even in well conducted responses, particularly if there is a marked increase in respiratory frequency over the course of the response. We were careful to avoid low initial FI_{CO_2}; PE'_{CO_2} for our subjects' responses increased virtually linearly with time; and, of our subjects, the one who gave the most linear responses also showed the greatest increase in respiratory frequency during a response.

The minor deviations from linearity shown by our subjects do not give a non-linear description any advantage. Non-linear description generally increases both the number of variables required to describe a carbon dioxide response and the complexity of their interpretation (fig. 2). If carbon dioxide

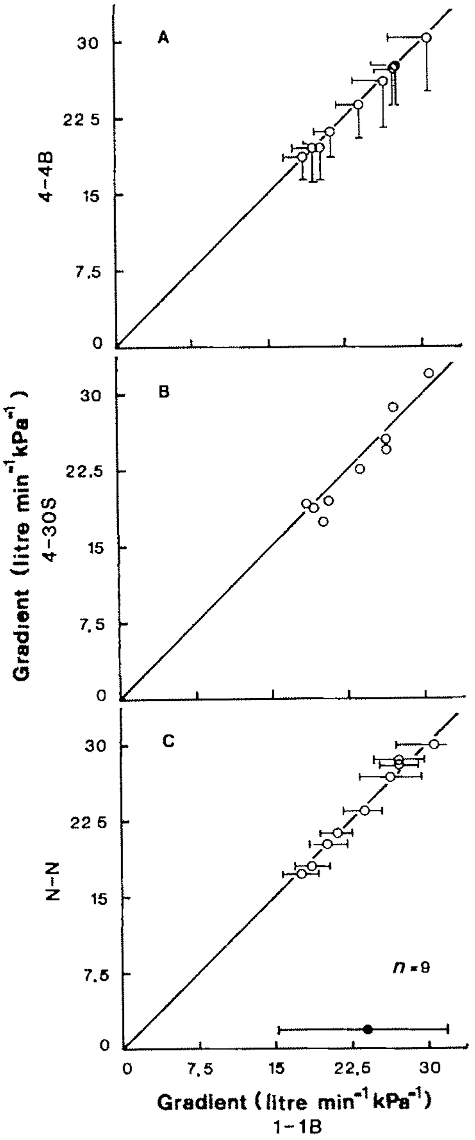

FIG 3. Ventilatory response to carbon dioxide by rebreathing, subject C.A. X axis: the gradients (litre min^{-1} kPa^{-1}) calculated breath-by-breath analysis (1–1B) from nine rebreathing manoeuvres; Y axis gradients for the same responses calculated by grouping breaths before analysis. The diagonal lines are the lines of identify. A. Every four breaths group (4–4B), bars indicate the 95% confidence limits of that gradient (t × SE) by 1–1B analysis (horizontal bars) and 4–4B analysis (vertical bars). B Grouping of the first four breaths of successive 30-s intervals (4–30S). C Grouping by averaging in blocks over each third of the response (N–N) Horizontal bars indicate the ±95% confidence limits by 1–1B analysis. Filled circle and bars at the bottom of the figure indicate the mean ±2 × SD (1–1B) for the nine responses.

responses are to be used to identify a change in central carbon dioxide sensitivity between one state and a number of others, it is convenient to have a single index or variable which adequately characterizes the change. Linear regression analysis yields two variables, the gradient and the intercept of the regression line. The gradient is the sensitivity, or gain: the rate of change of ventilation with $P\text{E}'_{\text{CO}_2}$. The intercept has the characteristics of a threshold, or zero offset. The intercept is sensitive to whether the response has been obtained in the steady-state or in the dynamic conditions of rebreathing; the gradient is not so affected (Read, 1967). Thus, it is common to use the gradient alone. The ventilation expected from the regression line at $P\text{E}'_{\text{CO}_2}$ 7.3 kPa (55 mm Hg) is sometimes used in an attempt to combine the effects of changing intercept and gradient, although it is possible with this approach to confound the effects of independent changes in two variables which are opposite in effect. We have, like others, concentrated on the gradients—with a particular interest in whether the method of analysis alters the estimate of within-subject performance variability from a given set of ventilation and $P\text{E}'_{\text{CO}_2}$ data, as was suggested by Strachova and Plum (1973).

Confidence limits within an individual response

The linear regression analysis for a given set of data finds the best estimate of the gradient of a line which must pass through the mean values of the dependent and independent variables. That estimate is accompanied by a measure of its reliability, commonly either its standard error or else the 95% confidence limits (t × SE) within which one might expect the best estimate to lie.

The different types of grouping in the 4–4B, 4–30S and N–N analyses each reduced the number of $\dot{V}\text{I}/P\text{E}'_{\text{CO}_2}$ data points used for the linear regression. The consequent reduction of degress of freedom (data points minus 2) had the effect of widening the standard error and 95% confidence limits attached to each best estimate (without much altering the numerical value of the best estimate). The average 95% confidence limits by the 1–1B analysis were approximately 10% of the average gradient, increased to between 13 and 16% for the 4–30S analysis and to well above 100% for the N–N analyses. Thus, the 1–1B analysis is the most powerful because it supplies the estimate of gradient which can be treated with the most confidence. Even so, if one has only two estimates of gradient, from one baseline and one experimental test in a single subject, one is quite likely to require a difference of gradient in excess of 20% of control to be able to state with any confidence that any difference actually exists.

Within-subject performance variability

The variability of the response between performances by an individual subject is assessed from the variability within a *group* of best estimates obtained from a single subject under standard conditions. It can be presented as the coefficient of variation about the group mean (Strachova and Plum, 1973), which assumes implicitly that the standard deviation of a group of gradients tends to increase with the mean. The reasons for the within-subject performance variability have been demonstrated and discussed by others (Read, 1967; Menendez-Cordova et al., 1976; Rebuck, 1976; Mustchin, 1977; Rigg et al., 1977; Sahn et al., 1977; Jordan, 1982), but they are still largely unknown. Most authors have found that the variability between days is greater than the variability within a day for any one subject. Although this was possibly true for our subjects, their gradients did show overlap between days and the mean results for each subject take no account of different days. One would need to perform more tests each day than were undertaken in this study to be certain of a change of mean gradient between days. Strachova and Plum (1973) implied that one source of variability was the method of analysis. They found smaller coefficients of variation using breath-by-breath analysis than had other workers using various types of grouped analyses. These analyses, however, were of different sets of data from different subjects. We applied a range of different methods of analysis to the *same* sets of data from the *same* subjects. Because there was generally close agreement between the individual estimates, irrespective of method (fig. 3A, B, C) there was also a close agreement between the coefficients of variation (table II). Agreement with the 1–1B analysis was least good using the 4–30S analysis, which grouped the first four breaths of successive 30-s periods of the response. This was partly because of information lost from the end of a response which did not last an exact number of half-minutes.

Thus, for repeated responses from a single subject, the estimate of within-subject performance variability was independent of the method of analysis. However, with the most powerful analysis (1–1B), the estimate was from a sample of gradients the values of which were known to fall within narrow limits. With the least powerful method (N–N), the estimate was from a sample of similar individual values many of which cannot confidently be distinguished from zero.

The paradox is immaterial when repeated estimates have been made. The values obtained by *any* method of analysis become sets of data in their own right. Statistical descriptions can be applied to the group which are independent of the descriptions of the individual values. These allow one *sample* of estimates to be compared with another *sample*.

The practical consequence of this is that, at least in sophisticated subjects, a good estimate of individual gradients and variability of gradients should be obtainable by any of a variety of averaging techniques, including graphical averaging obtained from a slow-running two-channel recorder, or an X–Y plotter. What is important is the conduct of the test (Rebuck, 1976; Jordan, 1982) and the sophistication of the subjects (Goodman and Black, 1985). A single estimate of gradient so obtained cannot necessarily be compared confidently with another single estimate, but two *groups* of gradients can. When only single estimates of gradient are available for each experimental state, the most powerful method, that is, the 1–1B analysis, is the method of choice. These matters are considered further in the following paper.

CONCLUSION

The simplest and quickest analysis is satisfactory for analysing the ventilatory response of sophisticated subjects to carbon dioxide although, if one has a computer to collect the data, it is sensible to analyse breath-by-breath. There is no reason to change from the established practice of using least squares linear regression.

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ANALYSES OF THE VENTILATORY RESPONSE TO CARBON DIOXIDE

Implications for Clinical Research

N. W. GOODMAN AND A. M. S. BLACK

SUMMARY

Baseline control estimations of the ventilatory response to carbon dioxide by the rebreathing method were attempted in 92 patients. When analysed retrospectively, only 53 were both technically and statistically satisfactory, although even these gave rise to some doubts. As the breath-by-breath correlation between ventilation ($\dot{V}_I$) and end-tidal carbon dioxide ($P_{E'CO_2}$) decreased there was a tendency for the gradients to become suspiciously low and for the estimates in an individual gradient to become sensitive to the method of analysis. Even so, when responses were grouped according to correlation, the method of analysis did not alter the mean gradient within a group. Single estimates of the carbon dioxide response at each stage of a study may not be a very powerful technique in clinical research; multiple estimates, if they can be arranged, would be more satisfactory.

In the previous paper (Goodman and Curnow, 1985), we have discussed the use of the rebreathing technique (Read, 1967) to measure the ventilatory response to carbon dioxide in sophisticated volunteers when circumstances allowed repeated estimates of the response characteristics in a standard state. However, although Read's technique brought the carbon dioxide response within the reach of many clinicians (Kafer and Marsh, 1977; Jordan, 1982), frequently the anaesthetist is unable to make more than one observation in any given state, and there is often insufficient time to train volunteer patients to achieve a technically optimal performance in the rebreathing manoeuvre. In this paper, we have studied some of the implications of performing carbon dioxide rebreathing tests under such circumstances.

PATIENTS AND METHODS

We examined retrospectively tests of the ventilatory response to carbon dioxide which had been carried out over a period by several investigators on 92 conscious patients. They were baseline observations of each patient's "normal" ventilatory response obtained during a number of clinical trials on the effects of certain drugs on ventilation in the perioperative period. All the studies had been approved by the district ethics committee. The carbon dioxide responses were measured (Read, 1967) on the afternoon of the day before surgery. All patients were allowed a few minutes to familiarize themselves with the equipment, but there was rarely time to perform more than one complete rebreathing test.

The raw data, end-tidal carbon dioxide ($P_{E'CO_2}$) and breath-by-breath inspired minute volume, either collected automatically or entered manually, were analysed along the lines described previously in sophisticated subjects, using different groupings of breaths for analysis (Goodman and Curnow, 1985): every breath (analysis 1–1B); consecutive groups of four breaths (analysis 4–4B); the first four breaths in each 30-s period (analysis 4–30S); and blocks of breaths that divided the response into three equal parts (analysis N–N). For each type of analysis the program applied least squares linear regression statistics to estimate the slope of the response (litre $\text{min}^{-1}\ \text{kPa}^{-1}$), and the intercept on the carbon dioxide axis at zero ventilation.

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RESULTS

Of the 92 responses examined, only 53 are considered further in this paper. The others were discarded because the initial $F\text{I}_{\text{CO}_2}$ in the rebreathing bag was too low (Rebuck, 1976); there were obvious leaks into the circuit during rebreathing; the patient could not rebreathe for long enough; or there was no significant correlation between ventilation and $P\text{E}'_{\text{CO}_2}$. As in the accompanying paper (Goodman and Curnow, 1985), we shall consider in detail only the estimates of the *gradient* of the carbon dioxide response (although the general conclusions can also be reached in terms of its intercept) and, again, the 1–1B analysis will be used to examine the relation between estimates of gradient, correlation coefficient and confidence limits, and as a basis of comparison with the results from the 4–4B, 4–30S and N–N analyses.

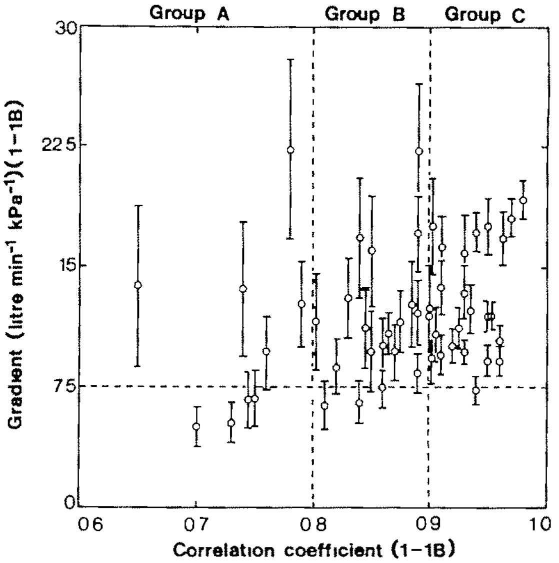

FIG. 1. Ventilatory response to carbon dioxide in 53 patients. Analysis of breath-by-breath $\dot{V}\text{I}/P\text{E}'_{\text{CO}_2}$ data points (1–1B) by least squares linear regression. Bars indicate the confidence limits (t × SE) attached to each estimate of gradient. Groups A, B and C are defined arbitrarily by the correlation coefficient (vertical dotted lines). Gradients below 7.5 litre min^{-1} kPa^{-1} are emphasized by the horizontal dotted line.

Validity of conventional least squares linear regression

For the responses showing the poorest correlation between ventilation and $P\text{E}'_{\text{CO}_2}$ we made estimates of the error variances in ventilation and $P\text{E}'_{\text{CO}_2}$ by performing separately regressions of each variable against time. The error variance in ventilation was always so much greater than the error variance in $P\text{E}'_{\text{CO}_2}$ that the y-on-x regression was close enough to the functional line, and we confirmed this using Bartlett's approximation technique (Davies and Goldsmith, 1976).

Gradient, correlation coefficient and confidence limits: 1–1B analysis

The 53 estimates of gradient by the 1–1B analysis are plotted (open circles) against the corresponding correlation coefficient, r, in figure 1. The vertical bars show the 95% confidence limits ($t \times$ SE) attached to each estimate. The vertical dispersion of the estimates within a range of r is the measure of the variability between subjects.

In figure 1, as the correlation coefficient (r) decreases there is a tendency for the gradient to decrease, with an increased likelihood of gradients less than 7.5 litre min^{-1} kPa^{-1} (1 litre min^{-1} mm Hg^{-1}); and there is a tendency for increased variability between subjects.

The widening of the 95% confidence limits on an individual gradient as correlation worsens is to be expected from the standard theory of regression and correlation:

$$\text{CL} = \frac{(b \times t)}{r} \times \left[\frac{(1-r^2)}{(n-2)}\right]^{\frac{1}{2}}$$

where CL is the confidence limits at a chosen level of probability, b is the gradient, r is the correlation coefficient and n is the number of observations that defines the number of degrees of freedom ($n-2$) to obtain the value of t. This theoretical relation between r and CL is shown for varying numbers of observations in figure 2.

There was also a tendency (not illustrated) for a low correlation to be associated with a low intercept on the carbon dioxide axis. The mean intercept for those lines with a correlation coefficient of 0.9 and above was 5.3 kPa and for those below 0.9 was 4.9 kPa ($P < 0.02$ by unpaired t test). The lowest intercept in the first group was 4.5 kPa; there were 10 intercepts lower than 4.5 kPa in the other group, the lowest being 2.3 kPa.

Comparisons with other methods of analysis

The impressions gained from figure 1 are strengthened by considering mean values of gradient, coefficient of variation and confidence limits after the data have been grouped by correlation coefficient (r). Group A consists of 25 estimates for which r was greater than 0.9, group B of 19 estimates for which r was between 0.8 and 0.899 and group C

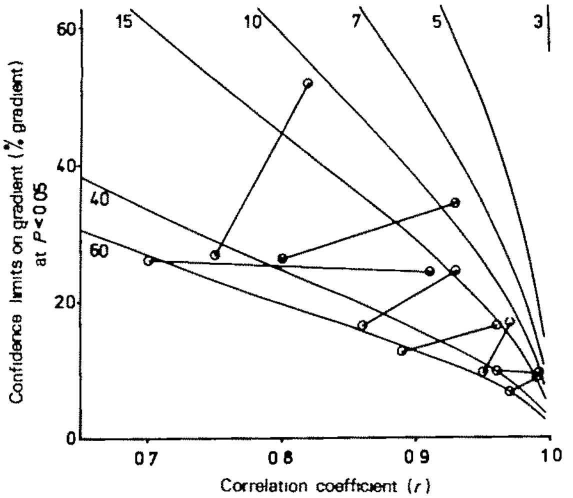

FIG 2 The relation between correlation coefficient and relative confidence limits on the gradient for differing numbers of observations. Theoretical relations (see equation in text) shown by the heavy lines, numbers indicate observations (degrees of freedom = $n - 2$). Experimental relations are from eight individual responses: the left-hand point analysed every breath (1–1B), the right-hand point the same data analysed by grouping every four breaths (4–4B). The lines between each pair of points are for clarity only and do not represent a progressive decrease in n.

of nine estimates for which r was less than 0.8 (figure 1).

The top line in table I shows that, for the 1–1B analysis, the mean gradient decreases, the coefficient of variation (the between-subject variability) increases and the mean confidence limits widen as mean r decreases from group A to group C.

The other three lines show the corresponding mean values obtained by the 4–4B, 4–30S and N–N analyses. The mean estimates of gradient within each group (A, B or C) and the coefficients of variation (estimates of between-subject variability) are little affected by the method of analysis. However, the mean r values increase and the mean confidence limits widen in the order 1–1B < 4–4B < 4–30S < N–N. The changes caused by the method of analysis are most striking in group C and least striking in group A. The change in correlation coefficient and confidence limits from 1–1B to 4–4B analysis is shown in figure 2 for eight of the responses, chosen to give a range of r, superimposed on the theoretical relation. Grouping almost invariably improves the correlation, but the confidence limits are not always widened. When r by 1–1B is already close to 1, there can be little increase of r by 4–4B analysis, but when it is low there may be a considerable increase. With 4–4B analysis, as r decreases, the relative confidence limits widen more dramatically than they do with 1–1B analysis, reflecting that the theoretical lines in figure 2 are steeper with fewer degrees of freedom. The changes in both correlation coefficient and confidence limits were more pronounced with the 4–30S analysis and especially the N–N analysis (not illustrated) when the confidence limits frequently exceeded 100%, that is, statistically the gradient was not distinguishable from zero.

Figure 3 shows that there is a fair measure of agreement between individual estimates of gradients analysed 1–1B or N–N. The agreement is even better with the 4–4B analysis (not illustrated), but not for the 4–30S analysis (not illustrated) despite the agreement between the mean estimates (table I). Disagreement is more likely when the 1-1B correlation coefficient is lower.

DISCUSSION

The validity of linear regression

In investigating the relationship between two variables x and y, one can estimate the regression of y-on-x or of x-on-y. Regressing x-on-y will give a steeper relation of change of y with x than regressing y-on-x: in the limit, zero correlation will give a gra-

TABLE I. *Ventilatory responses to carbon dioxide by the rebreathing technique: the effect of grouping breaths for analysis on mean gradient (litre min^{-1} kPa^{-1}) coefficient of variation (CV), mean correlation coefficient* (r) *and mean confidence limits (CL). Analysis by least squares linear regression taking different groupings of breaths for each graph point: every breath (1–1B); successive groups of four breaths (4–4B); four breaths from the beginning of successive 30-s periods (4–30S); blocks of breaths from each third of the response (N–N). Groups A, B and C defined by the correlation coefficient calculated from 1–1B analysis*

	Group A ($n = 25, r > 0.9$)				Group B ($n = 19, r > 0.8$)				Group C ($n = 9, r < 0.8$)			
Analysis	Mean	CV	r	CL	Mean	CV	r	CL	Mean	CV	r	CL
1–1B	12.8	25.9	0.93	1.4	12.2	35.2	0.86	2.9	10.5	47.5	0.74	2.9
4–4B	13.5	26.5	0.98	2.0	12.2	35.2	0.95	3.3	10.9	53.8	0.85	5.0
4–30S	12.5	28.3	0.98	2 6	12.1	37.9	0.96	5.4	10.0	51.9	0.88	6.7
N–N	12.8	27.6	0.99	15.1	12.6	35.1	0.99	22.0	10.9	59.3	0.92	53.5

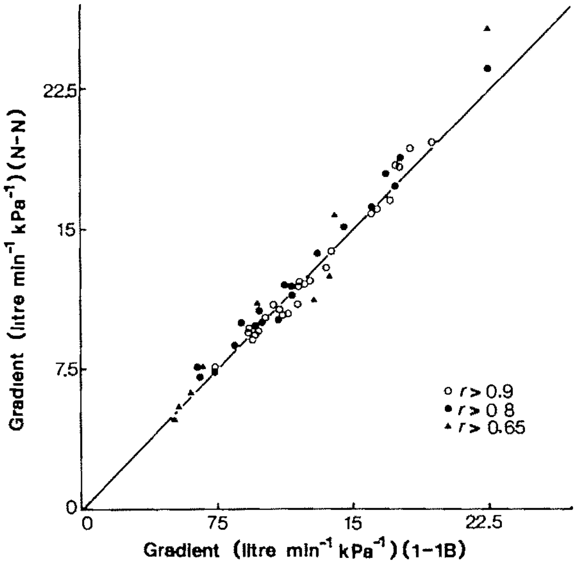

FIG 3. Agreement between the gradients (litre min^{-1} kPa^{-1}) of the carbon dioxide response calculated by block analysis (N–N) with those calculated by breath-by-breath analysis (1–1B). Symbols indicate differing correlation as shown.

dient of infinity or zero. Only when correlation is perfect ($r = 1$) will the two lines be identical. We were interested in the functional linear relation between ventilation and $P\mathrm{E}'_{\mathrm{CO}_2}$ and that must be somewhere between the two possible regression lines, determined by the ratio of the error variances in the ventilation and $P\mathrm{E}'_{\mathrm{CO}_2}$ (Davies and Goldsmith, 1976). There is far more error in the ventilation, not in its measurement but in the actual ventilation produced by a given $P\mathrm{E}'_{\mathrm{CO}_2}$ in a particular breath and, although strictly the more complex equations should be used, this validates the use of the y-on-x regression as the functional line.

We shall concentrate on the results of *linear* regression analysis as discussed in the accompanying paper (Goodman and Curnow, 1985), and particularly on the reliability of the estimates of gradient that this gives. Sources of major non-linearity were excluded in the selection of the 53 responses from the original 92.

The correlation coefficient is commonly used as the index of the reliability of the results of a rebreathing response to carbon dioxide. Correlation is a measure of the *association* between two variables and strictly is not appropriate because the ventilation *depends upon* the $P\mathrm{E}'_{\mathrm{CO}_2}$—the rationale for using regression analysis (Altman, 1982a). However, the two methods of analysis are mathematically equivalent and the correlation coefficient is frequently quoted in studies of rebreathing (Vejlsted, Hansen and Jacobsen, 1977; Rigg, 1978; Jordan, 1981; Camporesi et al., 1983). Mustchin (1977) suggests that a result should only be accepted if there is a "high correlation between the two sets of variables" (ventilation and $P\mathrm{E}'_{\mathrm{CO}_2}$), but he defines no numerical measures or limits.

However, the actual value of r for a particular rebreathing response depends on the method of analysis and this general rule is illustrated by our data in figure 2 and table I. Simply giving r values as validation, which many authors do, is not ideal. One can have a high r value which is nonetheless barely significant, implying that the corresponding gradient of the response can only just be distinguished from zero. The important statistic is the level of significance and the best way of expressing this is to relate it to the calculated gradient—by giving the confidence limits of the gradient. One can then judge whether an estimate of gradient is different from another estimate obtained at a different time and under different conditions.

The confidence that one can place in a particular rebreathing test must be based on both technical and statistical considerations: satisfactorily narrow *statistical* confidence limits do not necessarily guarantee that the response has been technically satisfactory. Of the 92 responses originally examined, a number were rejected as obviously invalid for technical reasons. Twenty were rejected because of leaks at the mouthpiece. These were more likely during hypercapnic hyperventilation in edentulous patients, whether or not they were wearing dentures. Large leaks were obvious from the paper record because the end-tidal carbon dioxide would decrease suddenly. Smaller leaks could be identified from periods in the record where the *measured end-tidal* $P\mathrm{CO}_2$ remained constant or increased more slowly than previously. Since ventilation continued to increase, presumably in association with a *cerebral* $P\mathrm{CO}_2$ which continued to increase, such leaks tended to give responses, or portions of responses, which were unduly steep. However, it was worrying that a number of responses in which intermittent leaks were clearly identified gave carbon dioxide responses with perfectly believable gradients and high correlation coefficients.

Conversely, there were many responses with low correlation coefficients for which there was no obvious technical fault. Those for which r was not significantly different from zero were, rightly or wrongly, excluded from further consideration. In the remainder, there was a worrying tendency for low correlation coefficients to be associated with low estimates of gradient (fig. 1). Of the identifiable technical faults, leaks at the mouthpiece or inadequate initial $F\mathrm{I}_{\mathrm{CO_2}}$ in the rebreathing bag should lead to a steepening of the response: leaks by steepening the response artificially; low carbon dioxide by causing a dog-leg and a real, late, steepening of the response. The overall gradient after a low initial $F\mathrm{I}_{\mathrm{CO_2}}$ would be too low if the portion before the dog-leg were not excluded. Hyperventilation before and at the start of rebreathing (Gilbert et al., 1972) would cause apparent flattening of the response, but in the present study, the low estimates of gradient were not associated particularly with hypocapnia in the period immediately preceding the test.

If the functional line lies midway between the two regression lines, then a low correlation will produce a falsely low gradient when estimated from *y*-on-*x* least squares. We showed, at least for our most critical group with low *r* values, that the *y*-on-*x was* the functional line and so the low gradients and intercepts were not a *statistical* result of low correlation.

Thus, the lower gradients in figure 1 are a real result of the poor correlation and might not represent the true carbon dioxide responses of the patients. The poor correlations seem likely to be the result of irregularities of breathing during the performance of the test, arising from additional unidentified drives to ventilation.

This supposition was supported by the subsidiary observation that, in a number of patients whose gradients were low in the control period (less than 7.5 litre min^{-1} kPa^{-1}), the gradients were *increased* in the experimental period after the administration of CNS and respiratory depressant drugs. Such increases were rare in patients whose control responses showed good correlation between $\dot{V}\mathrm{I}$ and $P\mathrm{E}'_{\mathrm{CO_2}}$, and gradients in the normal range.

Gradients lower than 7.5 litre min^{-1} kPa^{-1} are unusual. They have been reported (Read, 1967; Rebuck and Read, 1971; Irsigler, 1976), and they could be variants of normal. However, the combination of a low gradient and a low intercept on the $P\mathrm{E}'_{\mathrm{CO_2}}$ axis has disturbing implications. The intercept is not reported as frequently as the gradient. It is normally about 5.3 kPa and the lowest that Read (1967) reported was 34 mm Hg (4.5 kPa). From his figures there is no correlation between gradient and intercept. In his later study (Rebuck and Read, 1971) there was a weak negative correlation, but only if one included the two quoted gradients below 1 litre min^{-1} mm Hg^{-1} (7.5 litre min^{-1} kPa^{-1})—for which the confidence limits were ±45–50% of the gradient. In our study, for the responses showing the best correlation between ventilation and $P\mathrm{E}'_{\mathrm{CO_2}}$, there was no relation between intercept and gradient. One can get an idea of the position of a carbon dioxide response by calculating the predicted $P\mathrm{E}'_{\mathrm{CO_2}}$ at a "normal" ventilation of 5 litre min^{-1}. In our responses with low correlations, low intercepts and low gradients, this value tended to be well below the normal range of $P\mathrm{E}'_{\mathrm{CO_2}}$. If anything, one would expect a rebreathing carbon dioxide response to give a rather high calculated $P\mathrm{E}'_{\mathrm{CO_2}}$ at resting ventilation because the rebreathing method gives a relation between ventilation and $P\mathrm{E}'_{\mathrm{CO_2}}$ to the right of that defined by the steady-state method (Read, 1967). Irsigler's (1976) mean intercept was lower than Read's (for rebreathing), but Irsigler saw intercepts as low as −4 mm Hg (−0.5 kPa), associated with gradients for which the highest possible calculated $P\mathrm{E}'_{\mathrm{CO_2}}$ at a ventilation of 5 litre min^{-1} was about 0.8 kPa.

Measurements of ventilatory function are particularly prone to alterations by extraneous factors, although less so in sophisticated volunteers. Reviewers of the rebreathing method (Rebuck, 1976; Mustchin, 1977; Jordan, 1982) stress the precautions which should be taken to standardize the conditions for the test, and recommend that a number of responses should be performed at each stage of the study (Menendez-Cordova et al., 1976) — partly to train the subjects and partly to provide a group mean which will be a better estimate of the carbon dioxide response.

From our results, when the correlation by 1–1B analysis is poor, there tends to be a greater increase in *r* with the grouped analysis, because any grouping reduces variability, and a greater disparity between the estimates of gradient produced by the different analyses. The good agreement between the estimates which we found in our sophisticated subjects (Goodman and Curnow, 1985) was because, in them, the correlations were almost universally good. There is a danger that grouping breaths for analysis will conceal poor technique by giving an artificially high correlation, emphasizing that the confidence limits are the more valuable derived statistic.

It is difficult to arrange for patients to improve their performance by undertaking repeated carbon dioxide responses for each stage of a perioperative study. They are often admitted to hospital the day before surgery, and that day is largely occupied by the demands of routine clinical assessment and preparation. If one has estimates of gradient from only two responses obtained from one patient, one control and one experimental, the 95% confidence limits attached to each estimate are the only available measures by which one can decide whether the two responses are significantly different. If one is to minimize the chances of missing a real difference between the two responses, one should choose the most powerful method (i.e. breath-by-breath analysis) which will give the narrowest confidence limits on each estimate.

Even with the 1–1B analysis in sophisticated subjects the confidence limits tend not to be much less than ±10% and one is likely to require a difference in gradient well in excess of 20% in order to say that there is any difference at all between a single pair of responses. Confidence limits of ±10% imply r values of between 0.93 and 0.96 for responses based respectively on 60 and 40 data points (see theoretical lines in figure 2). Grouping these data points to give between 15 and 10 values for analysis requires a value of r of about 0.98 for ±10% confidence limits. With N–N analysis and only one degree of freedom r must be more than 0.997 to be significantly different from zero.

It is clear that a great deal may depend on obtaining a reliable value for the control gradient, and that such reliability is not to be obtained by asking unsophisticated subjects to perform only one rebreathing manoeuvre as a baseline in the control period. The response should be repeated if at all possible (Menendez-Cordova et al., 1976) although repetition may be less necessary in the experimental stages of a study if the disturbing influences of an intact consciousness are obtunded by CNS depressant drugs.

Although it is seldom feasible to repeat the steps of a perioperative plan of investigation sufficiently often, in each subject, to establish the *within-subject* variability at each step, these are repeated commonly in a series of subjects. The groups of carbon dioxide responses at each step then contain *between-subject* variability. It is common to allow for this by using a paired t test or an analysis of variance and this will establish whether there are statistically significant changes in carbon dioxide sensitivity between steps, without establishing reliably the average *sizes* of the changes. As with paired t tests under any circumstance, this should be done by quoting not only the mean changes in gradient between the steps, but also the standard errors of the mean changes.

The standard errors of the differences will be affected by all of the sources of variability which affected the estimates at each step of the investigation. For them to be sufficiently small to allow quantitative distinctions between drugs or doses of a drug, sufficiently large numbers of patients must be included at the design stage of the study.

It is unreasonable to approach a patient to give his time and co-operation if the design of the study and the methods used in it do not give it the power to make the distinctions which are being sought (Altman, 1982b). Only 53 of 92 control responses were even worth considering in this study. Of these a further number showed suspiciously poor correlation between $\dot{V}\text{I}$ and $P\text{E}'_{\text{CO}_2}$, although there was no obvious dividing line between the "acceptable" and the "unacceptable".

If one is interested primarily in determining whether drugs that are potentially depressant are safe in clinical practice, "it is more relevant to evaluate the action of clinically administered drugs on resting breathing in the undisturbed patient rather than on artificial challenges" (Jordan, 1982). For such purposes, the respiratory rate and the end-tidal $P\text{CO}_2$ might be perfectly acceptable and would be vastly more practicable (Jennett, Barker and Forrest, 1968; Engineer and Jennett, 1972; Jordan et al., 1979; Arunasalam et al., 1983).

It is different if one wishes to determine the natural history of a known depressant effect—its time course at particular sites of action. It is then appropriate to use more elaborate measurements, requiring trained volunteers and as much repetition as is required to achieve adequate definition, but one is left with the problems of extrapolating from the conditions of such studies to those of the clinical situation.

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choice, on the dorsum of the hand. The cream was covered with Blenderm tape 1523 (3M) or a thin plastic wrap, to form an occlusive dressing. The bandage was removed immediately before venepuncture and the skin inspected for any local reaction. After disinfection with 0.5% chlorhexidine in 70% ethanol, the cannula was inserted.

The degree of pain was marked by each volunteer on a 100-mm visual analogue scale (VAS) with a range from "no pain" to "painful". A new scale was used for each evaluation. Local reactions in the form of oedema, erythema and blanching were recorded on a four-point scale: none, slight, moderate or severe.

The intrasubject differences (mean VAS scores) between EMLA and placebo were tested by the Wilcoxon signed ranks test. For the analysis of differences of application time, the paired *t* test was used.

RESULTS

Results from 31 volunteers (24 female) (median age 31 yr, range 18–48 yr) were analysed. The median number of EMLA applications per subject was 5 (range 2–5) and for placebo 3 (range 1–3). Nine subjects did not complete the study because of administrative problems such as holidays, sick-leave etc. No subject was excluded from the study because of adverse reactions to the treatment.

Of the 220 applications, 81% were in the cubital fossa, 15% on the dorsum of the hand and 4% on the lower arm. There was no difference between EMLA and placebo in regard to the duration of application. In total, there were 140 applications of EMLA and 80 with placebo. EMLA was superior to placebo in all but three volunteers, in whom both preparations produced similar effects (fig. 1). The individual pain scores after application of placebo cream were scattered over the whole scale, while the majority of scores after EMLA were near the "no pain" end of the scale, indicating a decrease in the pain experienced with the active formulation.

The between subject differences in mean pain score between EMLA and placebo are presented in figure 2. Treatment with EMLA resulted in significantly lower mean pain scores ($t = 4.74, P < 0.001$).

Transient local skin reactions after both EMLA and placebo consisted of blanching, erythema and, in a few patients, oedema at the site of application. The reactions were almost equally distributed between active and placebo treatments (table I) and did not increase in severity with repeated application.

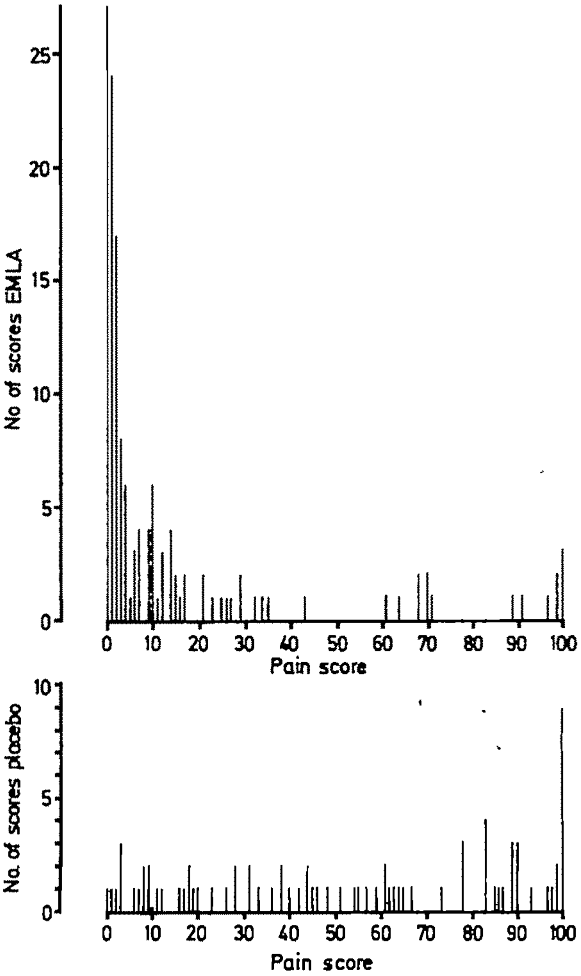

FIG 1. Distribution of pain scores on the visual analogue scale with EMLA (n = 140) or (n = 80) placebo.

DISCUSSION

The present investigation in adult, unpremedicated volunteers confirms the analgesic effect of EMLA cream noted in other studies (Ehrenström-Reiz and Reiz, 1982; Hallén and Uppfeldt, 1982).

In our previous study in children (Hallén and Uppfeldt, 1982), the evaluation of the degree of pain was made, by nurses, on a three-point verbal scale.

TABLE I. *Number of volunteers with local skin reactions at the area of application*

	EMLA	Placebo
Blanching	26	19
Erythema	10	8
Oedema	4	4

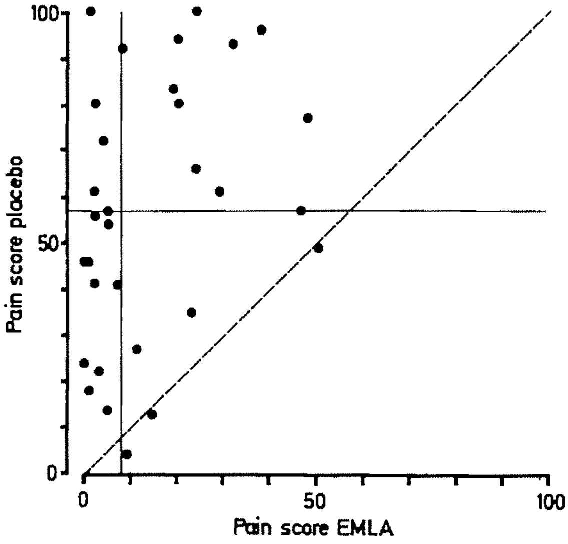

FIG 2. The relationship between individual mean pain scores with EMLA or placebo. Each dot represents one person. Dots above the broken line show individuals with higher mean pain score with placebo than with EMLA. The thin horizontal and vertical lines represent the median pain score after EMLA and placebo, respectively.

However, even that rather crude method showed a significant difference in favour of EMLA over placebo. In the present study a visual analogue scale was used to provide a more sensitive evaluation of differences in the pain experienced (Ohnhaus and Adler, 1975; Revill et al., 1976; Scott and Huskisson, 1976).

In adults, EMLA cream has been shown to penetrate the intact skin, and it has been used successfully as a topical analgesic for superficial skin procedures. The eutectic mixture of lignocaine and prilocaine was more effective than emulsions of either base alone. In the EMLA emulsion 80% of each droplet consisted of lignocaine and prilocaine, in contrast to only 20% active substance in the single component formulation. This was probably the main reason for the eutectic mixture being the more effective (Juhlin, Evers and Broberg, 1980).

We conclude that EMLA cream decreases substantially the pain produced by routine venous cannulation. Thus, the first experience of an anxious patient in the operating room need not be a painful venepuncture.

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A METHODOLOGICAL STUDY OF SPINAL (SUBARACHNOID) ANAESTHESIA IN THE RAT AND THE MOUSE

S. B. A. ÅKERMAN

Experimental models for spinal (subarachnoid) anaesthesia have been described in various animal species, including sheep (Lebeaux, 1975) and dog (Feldman and Covino, 1981). A technique in the monkey has been developed (Denson et al., 1981, 1982) which is of value in studying primate physiology and the pharmacology of spinal anaesthesia. There is a need, however, for a technique in small animals to permit the study of the efficacy of new local anaesthetic agents in relation to controls, and the basic problems of spinal anaesthesia. The present report describes the spinal anaesthetic effect of some commonly used local anaesthetics in the rat and mouse, following modifications to the techniques for intrathecal injection described originally by Yaksh and Rudy (1976) and Hylden and Wilcox (1980). The two methods may prove to be complementary to techniques in larger animals.

MATERIALS AND METHODS

Male Sprague–Dawley rats (Anticimex, Sweden) weighing 300–400 g were anaesthetized with methohexitone 40 mg kg^{-1} i.p. After removal of hair on the neck, an incision was made in the midline extending caudally about 1 cm from the occipital crest. A slit was made in the exposed cisternal membrane, followed by the insertion of a polyethylene catheter filled with lactated Ringer's solution. The catheter was advanced caudally in the subarachnoid space to the level of the lumbar enlargement, as described by Yaksh and Rudy (1976) and Yaksh and Wilson (1979). To avoid damage to spinal tissue, the diameter of the portion (9 cm) of the catheter (PE10) to be implanted had been decreased further by immersion in hot water and extension. The catheter was sutured to surrounding tissue. The skin incision was sutured or closed with Locktite. The external part of the catheter extended freely (7–8 cm) and its end was closed by heating.

Following the operation, and throughout the experimental period, the animals were housed singly in Macrolon cages on Torrax bedding (aspen wood cuttings, Anticimex, Sweden) with free access to food (rat pellets, Ewos AB, Sweden) and water. The animals were kept in a temperature-controlled (10–22 °C), ventilated (17 air changes per hour) and artificially lighted room with a relative humidity not less than 55%. All experiments described below were performed at room temperature (22 °C) between 8 a.m. and 3 p.m. The studies were approved by the Committee for Ethical Issues of the Swedish Board of Agriculture.

SUMMARY

Rat and mouse were utilized as models to study the spinal (subarachnoid) anaesthetic effects of five commonly used local anaesthetic agents. Duration and frequency of motor and sensory blockade, and onset time were determined after injection of 5.0% lignocaine, 0.75% bupivacaine and 1.0% amethocaine to the same groups of rats with chronically implanted catheters in the lumbar subarachnoid space. Dose–response curves for lignocaine, mepivacaine, bupivacaine, amethocaine and cinchocaine were obtained after single intrathecal injection to the mouse. The relative potency and other characteristics of the compounds investigated were in agreement with results obtained in other species, including man. The techniques described may provide useful adjuncts to methods in larger animals for the evaluation of potential new spinal anaesthetic agents, and the study of various factors that may influence spinal anaesthesia.

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Rat model

After a recovery period of 1 week, the rat was slightly restrained in a plastic holder and 5.0% lignocaine 20 µl injected at a rate of approximately 1 µl s^{-1} followed by lactated Ringer's solution 10 µl to flush the catheter of its content of drug. The anterior end of the holder was elevated to allow the injected solution to flow down the subarachnoid space, thereby avoiding rostral spread and possible toxic reactions. One minute after the end of the injection the animal was removed from the holder and the degree of local anaesthesia assessed. Complete motor blockade was defined as inability to stand on the hind-limbs. Complete sensory blockade was considered present if the animal did not vocalize or attempt to withdraw the hind-legs in response to pinching of the foot-pads with Allis tissue forceps. The time of onset and the duration of complete blockade, and the time taken to the return of normal motor and sensory function, were measured at regular intervals. In the present study, two of 10 operated rats displayed unilateral blockade and were excluded from further trials. Bilateral, reversible motor and sensory blockade followed the injection of lignocaine in the remaining eight rats and, at postmortem, was found to be directly correlated with proper positioning of the tip of the catheter in the subarachnoid space. In six rats, the injection of lignocaine was followed at 5-day intervals by the administration of 0.75% bupivacaine and 1.0% amethocaine, while two rats received repeated injections of saline. Finally, all animals received again 5.0% lignocaine with results that were not significantly different from the first experiment. Accordingly, all rats received four consecutive injections over a period of 4 weeks. The animals gained normal weight and there were no signs of abnormal behaviour.

Mouse model

Intrathecal injection in the mouse was carried out as described by Hylden and Wilcox (1980). Before spinal anaesthesia in the conscious animal (male NMRI mice, 20–25 g, Anticimex, Sweden), 0.1 ml of prilocaine 5 mg ml^{-1} was injected intracutaneously to produce dermal analgesia of the sacral region before a 1.0-cm cutaneous incision was made perpendicular to the vertebral column. A 30-gauge, 0.5-inch needle (B.D. Yale) connected to a 20-µl luer tip syringe (Hamilton) was inserted to the subarachnoid space. The local anaesthetic solution was injected to L5–6 in a volume of 5 µl. Inability to stand on the hind legs was taken as the criterion of complete motor blockade, and the mouse was considered recovered when it could walk and grip normally with the toes. After the time of onset of motor blockade was recorded, the skin incision was closed and the presence of blockade tested at regular intervals until normal function had returned. Signs of adverse reactions to the injection were recorded. Each compound was tested at varying concentrations in groups of eight or 10 mice.

The following local anaesthetics were used: lignocaine, mepivacaine, prilocaine, bupivacaine, amethocaine and cinchocaine. All agents were obtained from Astra Läkemedel AB, Sweden. Solutions of the hydrochloride salts were made in physiological saline on the day of the experiments with adjustment of pH to 6.5–7.0. Commercial lignocaine 50 mg ml^{-1} heavy spinal solution was used in the experiment in the rat.

Statistical significance was determined by means of Student's t test ($P \leqslant 0.05$).

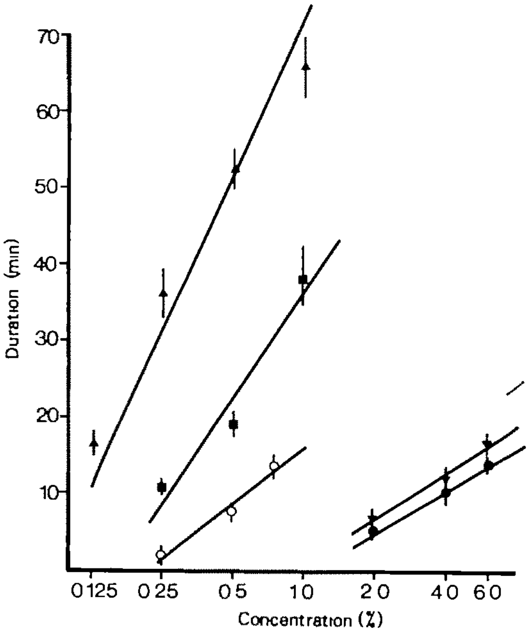

FIG 1. Spinal anaesthesia in the mouse. Duration (min) of motor blockade after injection of 5 µl of the test solution to groups of 8 or 10 animals. Each value is the mean ± SEM from 16 or 20 legs. ● = Lignocaine (n = 8); ▼ = mepivacaine (n = 8); ○ = bupivacaine (n = 10); ■ = amethocaine (n = 8) and ▲ = cinchocaine (n = 8).

TABLE I. *Spinal anaesthesia in the rat. Time (min) of onset and duration of blockade after subarachnoid injection of 20 µl of the test solution into a group of six animals. Each value is the mean ± SEM from 12 legs. Blockade was 100% except *11/12. Significant differences: †* v. *bupivacaine and amethocaine; ‡* v. *amethocaine; ††* v. *bupivacaine*

		Motor blockade			Sensory blockade		
		Complete block			Complete block		
Compound	Concn (%)	Onset	Duration	Duration to recovery	Onset	Duration	Duration to recovery
Lignocaine	5.0	1.2 ± 0.2	20.0 ± 1.1†	27.9 ± 1.3†	1.5 ± 0.1†	18.3 ± 2.8††	26.7 ± 2.6††
Bupivacaine	0.75	1.9 ± 0.3*	29.6 ± 2.7‡	35.4 ± 2.6‡	3.0 ± 0.6*	36.4 ± 6.4	47.7 ± 7.3
Amethocaine	1.0	1.6 ± 0.2	40.4 ± 4.2	50.4 ± 3.6	2.7 ± 0.4	27.9 ± 3.6	30.8 ± 4.1

RESULTS

The subarachnoid injection of 5.0% lignocaine 20 µl,0.75% bupivacaine 20 µl or 1.0% amethocaine 20 µl to rats produced spinal anaesthesia in a readily reproducible manner. The duration of motor blockade increased in the order lignocaine, bupivacaine and amethocaine (table I), the duration of motor blockade with amethocaine being about twice as long as that with lignocaine. In regard to sensory blockade, bupivacaine gave the longest duration of action, and lignocaine the shortest.

The onset of blockade with amethocaine and bupivacaine was similar, but took somewhat longer than lignocaine. All blocks were completely reversible and there were no overt adverse reactions.

The local anaesthetics studied were of two categories in regard to spinal anaesthetic potency (motor block) in mice (fig. 1). One group consisting of lignocaine and mepivacaine had the minimum blocking concentration at 2.0%, which resulted in blockade of a short duration. Only a short prolongation of the duration of action was seen when the concentration was increased to 6.0%. The other group of compounds, consisting of bupivacaine, amethocaine and cinchocaine, displayed higher activity with minimum blocking concentrations at 0.125–0.25%. The compounds showed profound differences in their dose–duration curves (fig. 1). The slope of the curve for bupivacaine was similar to those of mepivacaine and lignocaine. The duration of motor blockade following 0.75% bupivacaine was not significantly different from that of 6.0% mepivacaine and lignocaine, respectively. Amethocaine was clearly longer-acting than bupivacaine at equal concentrations. Cinchocaine had the lowest threshold concentration for blockade and produced the longest duration of blockade of the compounds tested. The onset time to blockade decreased dose-dependently with the exception of lignocaine (fig. 2), which also had the fastest onset, followed by mepivacaine. The more active and long-lasting compounds showed slower onset times.

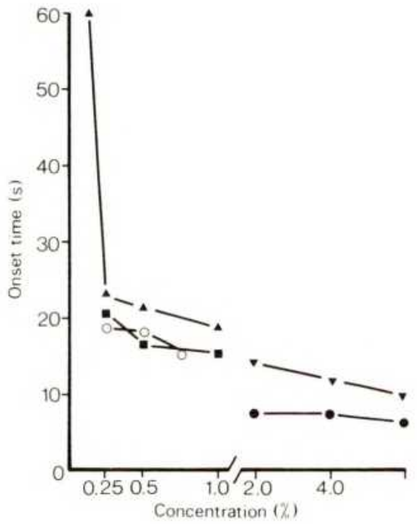

FIG. 2. Spinal anaesthesia in the mouse. Mean time of onset (s) of motor block. Injected compounds: ● = lignocaine, ▼ = mepivacaine, ○ = bupivacaine, ■ = amethocaine and ▲ = cinchocaine.

Cinchocaine was the only agent that showed observable side-effects on spinal injection in mice. The animals reacted by jumping and scratching as well as biting the hind-quarters as signs of local irritation. With 1.0% cinchocaine, CNS-toxicity in the form of a transient loss of the righting reflex was recorded.

DISCUSSION

The relative potency and other characteristics of the compounds used in the present study in the rat and mouse compare well with results obtained with subarachnoid anaesthesia in other species, such as sheep (Adams and Doherty, 1977), dog (Feldman and

Covino, 1981) and man. In the mouse, cinchocaine required the lowest dose for satisfactory blockade, closely followed by amethocaine and bupivacaine, while lignocaine and mepivacaine were less potent. The duration of motor blockade was longest with cinchocaine, followed in order of decreasing duration by amethocaine, bupivacaine, lignocaine and mepivacaine. A relatively short-acting agent such as lignocaine had a more rapid onset than the more long-acting compounds. Another similarity with clinical experience was the propensity for sensory blockade with bupivacaine, as shown by the experiments in the rat. Thus, the spinal anaesthetic properties in the rat and mouse appear qualitatively similar to those in other species, despite differences in absolute values, for example for latencies and durations.

The technique in the rat has the advantage that comparative studies can be performed in one and the same animal, allowing evaluation of both sensory and motor blockade. With the rat preparation, the tip of the catheter is not always localized dorsally in the subarachnoid space. For example, unilateral blockade by a local anaesthetic was mostly associated with a lateral position of the tip of the catheter at postmortem. It is difficult completely to avoid immediate failures such as unilateral blockade, but in our experience the frequency of successful blockade is around 80%. We have found that the injection of lignocaine which results in a bilateral, reversible blockade is a good test of a successful preparation before rats are used in further studies of spinal systems that mediate nociception and antinociception (Åkerman, Rosell and Folkers, 1982). Rats tolerate the chronic catheter well. The animals used in the present study had useful functioning catheters over a period of 4 weeks, during which time test solutions were injected four times without problem.

The technique in the mouse seems to be of particular value for the rapid determination of blocking properties of potential new spinal local anaesthetics relative to reference compounds, and structure–activity relationships. Information about sensory blockade was gained in the rat, but not in the mouse, from the degree of inhibition of the withdrawal response to pressure to the foot-pads. Results of preliminary studies (Åkerman et al., unpublished observations) indicate that, in both species, inhibition of the tail-flick response to painful heat can be used as an alternative to pressure as an indication of blockade of sensory modalities by local anaesthetic agents.

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RESIN INJECTION STUDIES OF THE LUMBAR EXTRADURAL SPACE

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SUMMARY

Two resin injection studies of the lumbar extradural space were performed to elucidate its size and shape. To counteract the lack of cerebrospinal fluid pressure in the cadaver, the subarachnoid space was filled with water. In group 1, the extradural injection of resin caused an immediate increase in subarachnoid pressure. The casts produced varied in thickness, but were situated predominantly in the dorsomedial and dorsolateral regions of the spinal canal. Thin anterior spread occurred in 40% of cases. In group 2, resin was injected to the subarachnoid space before the extradural injection of dyed resin. The resulting extradural casts were thinner than in group 1, but the distribution of resin was similar. The problems of interpreting resin casts are discussed in relation to the results obtained, with reasons for suggesting that the extradural space is only potential.

A previous resin injection study of the lumbar extradural space (Husemeyer and White, 1980) suggested that the dural sac was triangular with a posterior midline fold, and implied that the extradural space was quite broad in the dorsolateral and anterior regions. This did not agree with the picture of the extradural space in many textbooks of anatomy, where it is shown as a thin layer situated between the dura mater and the vertebral canal, containing fat and blood vessels. It is possible that the lack of cerebrospinal fluid (CSF) pressure in the cadaver (Barrison, 1933) affected the shape of the resin casts. Therefore, resin injection studies were performed in which attempts were made, in the cadaver, to compensate for these postmortem changes.

MATERIALS AND METHODS

The studies were performed upon two groups of 10 cadavers, aged at death between 65 and 95 yr. The cadavers used, donated to the anatomy department for teaching and research, were at least 48 h postmortem, to comply with the regulations of the Anatomy Act (1832 and 1871).

In both groups a 16-gauge Tuohy needle was inserted to the extradural space at the 2nd or 3rd lumbar space, and an 18-gauge spinal needle, connected to a lumbar puncture manometer via a three-way tap, was inserted to the cisterna magna. Water 100–200 ml was injected to the cisterna magna to create a pressure in the subarachnoid space of 15–20 cm H_2O as measured by the manometer.

In group 1, 15 ml of resin was injected to the extradural space.

In group 2, 60 ml of resin was injected to the lumbar subarachnoid space through a 16-gauge needle, allowing the displaced intrathecal water to overflow from the cisternal manometer. Following this 15 ml of resin was injected through the needle in the extradural space. This resin had been coloured with a blue dye to distinguish it from that in the subarachnoid space.

The resin used was of low viscosity, suitable for the preparation of anatomical corrosion casts (Trylon Ltd, Wollaston, Northants, NN9 7QJ). When mixed, it had a pot life of 25 min, and it was injected 15 min before gelling occurred. The cadavers were then embalmed. Ten days later, the lumbar vertebrae were removed and transversely sectioned with a bandsaw. The casts were examined and measured *in situ*. The specimens were decalcified using concen-

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trated nitric acid, before dissection.

RESULTS

Group 1

In all cases, during the injection of the extradural resin, there was an immediate increase in pressure at the cisterna magna, and water overflowed from the manometer until the injection of resin was complete.

In all 10 cadavers, resin was seen only in the extradural space, predominantly in the dorsomedial or the dorsolateral region, or both (fig. 1). The maximum depth of the casts varied from 1 to 9 mm. In those cases in which the maximum depth was greater than 3 mm, there was local inward bulging of the dura mater as a result of the presence of a large globule of resin, from which a thin layer of resin spread out on either side (fig. 2). In these lateral projections the resin tended to be fragile, and often broke during dissection.

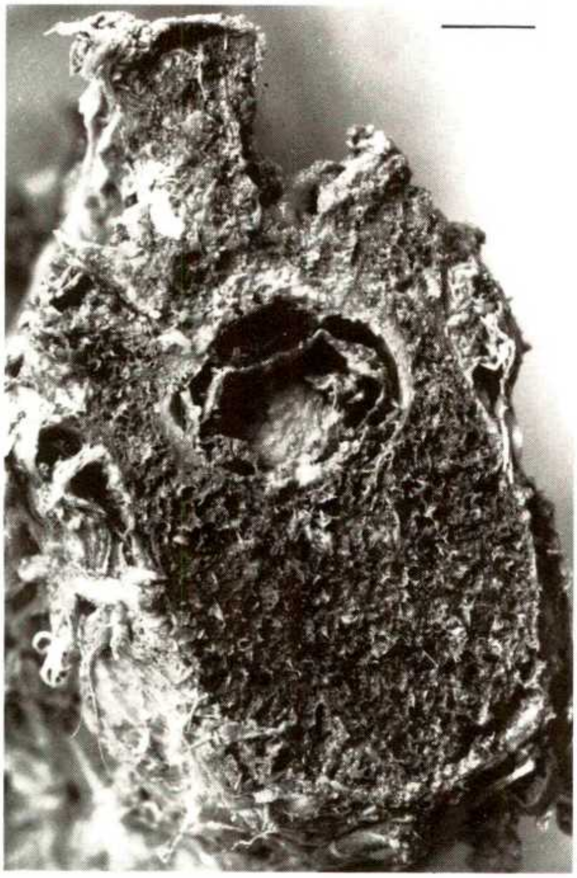

FIG. 1. Transverse section through first lumbar vertebra. The resin is seen in the extradural space posteriorly between the dura mater and the vertebral canal. (Bar = 1 cm).

In four cases the resin had spread in a very thin layer, less than 1 mm thick, in the region between the anterior dura mater and the posterior longitudinal ligament. On dissection this anterior layer was found to be incomplete, forming a network on the outside of the dura mater.

In none of the cases examined was the dural sac triangular, as previously described (Husemeyer and White, 1980), but it tended to conform to the shape of the resin injection cast. All casts had an undulated surface on the dural aspect, and none showed a dorsomedian fold of dura mater.

Group 2

All 10 cadavers contained clear resin in the subarachnoid space. The extradural space contained a thin layer of coloured resin which varied between 1.5 and 4 mm in depth (fig. 3), and was found in the region posterior to the intervertebral foramina. The maximum thickness of the resin tended to be in the midline posteriorly, spreading out and thinning laterally. In only four instances was there any spread into the anterior compartment, and again this was found to form an incomplete layer, as in group 1. In one case, the resin in the extradural space formed a bulge, as described in group 1. A dorsomedian fold of dura mater, 1 mm in depth, was found in one cadaver. The dural sac tended to conform to the shape of the spinal canal, and in no instance was the dural sac found to be triangular.

DISCUSSION

Whenever resin is injected to a closed space within the body, there will be some distortion of the tissues, which will be preserved in the form of a cast. By definition, casts are artefacts, but this does not necessarily imply inherent error, as it is merely a description of something that is introduced during preparation or investigation.

Various factors which affect the shape of the cast must be considered in interpreting the results; they include the area to which the injection is made, the compliance of the tissues, the viscosity of the resin and the volume of resin injected. Wherever resin is injected, it will flow along the lines of least resistance. If it is injected to an open area, such as a blood vessel, it will fill up the available space, but if it is injected to an area where there is no existing space, it will create one by causing distortion in the most compliant tissues. In the extradural region this is the dural sac, which is supported *in vivo* by CSF pressure, but is unsupported in the cadaver. It is possible

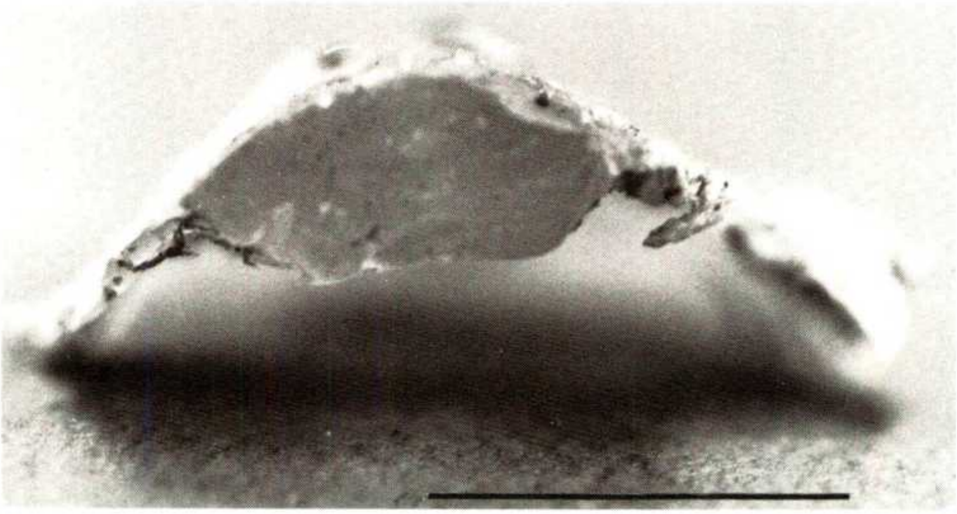

FIG. 2. Transverse section of resin cast showing large posterior midline bulge with thin projections extending anterolaterally on either side. (Bar = 1 cm).

for the injection of resin to cause distortion of only the inner border of the extradural space, as the outer border is composed of bones and ligaments, and is effectively non-compliant. The spread of resin will also be affected by its viscosity. When tissue distortion occurs, local forces may be created which will cause the resin to be redistributed to an extent related to its viscosity, which is a major factor in determining the flow of resin in response to an applied force. In addition, the viscosity increases as gelling progresses, so that there is only a limited time in which redistribution can occur. Finally, the amount of resin is important, as injecting an inadequate amount to a space will not fill up the available area, whereas injecting an excess to a potential space will cause considerable distortion of the tissues.

In the cadaver there is no CSF pressure (Barrison, 1933) and resin injected to the extradural space will collapse the dura mater. No local pressures will be created to cause redistribution of the resin, and the cast would be expected to show little more than the result of compressing the dura mater against the contents of the dural sac. When water was injected to the subarachnoid space of cadavers, creating a pressure of 15–20 cm H_2O, the compliance of the dura mater approached that found *in vivo*. Under these conditions the extradural injection of resin immediately caused water to flow out of the needle in the cisterna magna. This was an important observation, as it implied immediate dural distortion, and suggested that the extradural space was only potential. Were a space to have existed around the dura mater, it is unlikely that the immediate increase in pressure would have occurred, as there would have been room to accommodate the resin without distorting the dura.

Dural distortion will allow the formation of a depot of resin which will be subject to the effects of local forces (arising from the pressure of fluid in the subarachnoid space) tending to reform the original shape of the dura mater, and the resin will spread into a more even layer around it. However, if the time between the injection of resin and the point of gelling is short (as recommended by Tompsett (1970)), there will be little opportunity for the resin to spread. Both of these factors will tend to maintain distortion, and may explain the shape of the cast in figure 2. If resin is injected to the subarachnoid space, the compliance of the dura mater will be reduced, and the distortion produced by the subsequent extradural injection of resin will also be reduced. In this situation the final shape of the cast will depend, not only upon the above factors, but also upon the relative time of injection of the subarachnoid and extradural resins. If the extradural resin is injected when the subarachnoid resin has gelled, it will not distort the dura mater, but if the resin is injected to the extradural space when the subarachnoid resin is still pliable, as occurred during these studies, it will produce a distortion of the dura mater. This may be redressed by the effect of local forces as described above, but only until the subarachnoid resin has gelled.

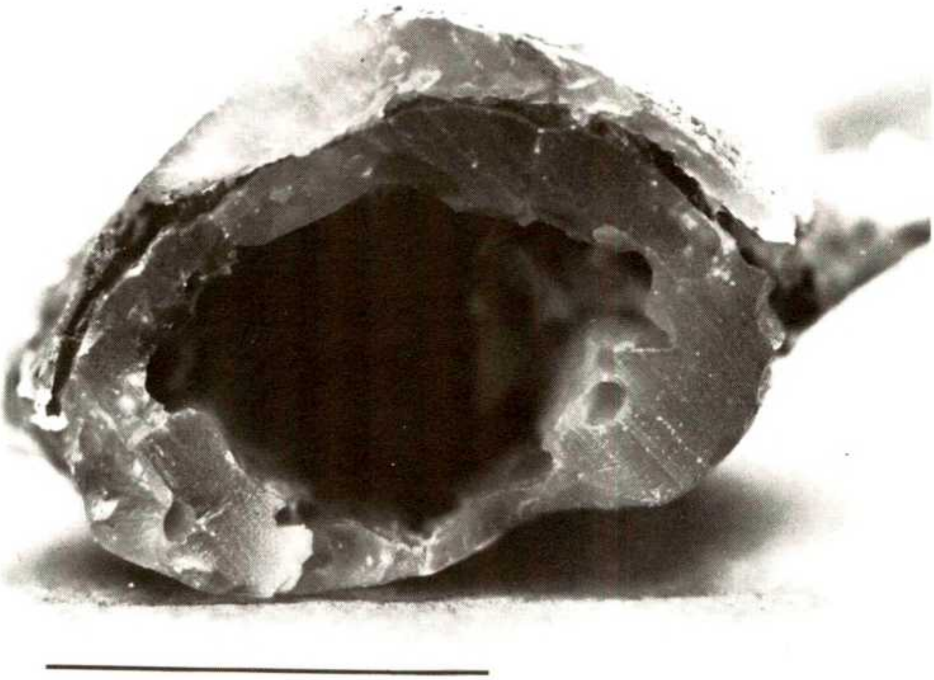

FIG. 3. Transverse section of resin casts. The resin in the extradural space is seen as a thin layer on the posterior aspect of the subarachnoid resin. (Bar = 1 cm).

The infrequent spread of resin into the region between the anterior dura mater and posterior longitudinal ligament further supports the suggestion that the extradural space is potential. In those cases in which there was no anterior spread, the dura mater was found to be closely applied to the posterior longitudinal ligament, and in the eight cases in which the resin had spread into the anterior compartment, it was very thin and incomplete. It is possible that this was the result of using too little resin. Determining the correct volume of resin to inject to the extradural space is difficult. Too little will not fill the space should it exist, but too much will cause excessive distortion of the tissues. Fifteen millilitre was chosen in these experiments, as it is similar to the volume of local anaesthetic used in extradural anaesthesia. Filling the subarachnoid space itself also may cause distortion, from within rather than from without. In the first group, distortion from within seems unlikely as the water-derived subarachnoid pressure was similar to that found *in vivo*. In the second group, in which resin contributed to the subarachnoid pressure, the argument for distortion from within is much stronger. In either case, it would be impossible for more resin to be accommodated by forcing the dura mater any further against the walls of the vertebral canal, if the extradural space is only potential.

It is not easy to reach any definite conclusions about the shape of the extradural space from the casts produced, as it was not possible to quantify the extent of distortion. However, the authors support the hypothesis that the extradural space is potential on the basis of two observations: (1) the extradural injection of resin caused water to flow out immediately from the needle in the cisterna magna (group 1); and (2) the paucity (or absence) of resin in the anterior compartment.

ACKNOWLEDGEMENTS

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TRANSCUTANEOUS ELECTRODES DURING ANAESTHESIA

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Conventional monitoring in paediatric anaesthesia includes the use of the precordial stethoscope, indirect measurement of arterial pressure, ECG and recording of body temperature. More complex monitoring such as direct pressure measurement by arterial cannulation and blood-gas determination are usually required in cardiac and other types of major surgery. However, these invasive methods may be hazardous and are not always appropriate for routine clinical use. Nevertheless it is necessary to be able to assess the adequacy of respiratory function during anaesthesia.

We have evaluated the use of transcutaneous oxygen ($P\mathrm{tc}_{\mathrm{O}_2}$) and transcutaneous carbon dioxide ($P\mathrm{tc}_{\mathrm{CO}_2}$) monitors. Thirty healthy non-premedicated children aged 4–14 yr were studied The electrodes (Kontron Medical) were calibrated and applied to the skin of the chest wall in the 3rd or 4th intercostal space. Following a stabilization period of 10–15 min, anaesthesia was induced with thiopentone 5 mg kg^{-1} and maintained with a volatile agent. Intubation was carried out 5 min later

Measurements of $P\mathrm{tc}_{\mathrm{O}_2}$ and $P\mathrm{tc}_{\mathrm{CO}_2}$ were made for 30 min before surgery and recorded on a Kontron writer. A sample of free flowing capillary blood was analysed at 5-min intervals

Statistical analysis of data involved the calculation of correlation coefficients between $P\mathrm{tc}_{\mathrm{O}_2}$ and $P\mathrm{cap}_{\mathrm{O}_2}$ and $P\mathrm{tc}_{\mathrm{CO}_2}$ and $P\mathrm{cap}_{\mathrm{CO}_2}$. Linear regression lines were calculated using least squares regression analysis.

Seventy-six pairs of simultaneous measurements of $P\mathrm{tc}_{\mathrm{O}_2}$ and $P\mathrm{cap}_{\mathrm{O}_2}$ were analysed. The correlation coefficient equalled 0.57 and the slope of the regression line was 0.38 ($P < 0.001$). Similar findings have been reported by Wimberley and colleagues (1983).

Ninety-nine pairs of simultaneous measurements of $P\mathrm{tc}_{\mathrm{CO}_2}$ and $P\mathrm{cap}_{\mathrm{CO}_2}$ were analysed. The correlation coefficient was 0.81 and the slope of the regression line was 0.93 ($P < 0.001$) There were consistent, although transient, reductions in $P\mathrm{tc}_{\mathrm{O}_2}$ during and following intubation and a persistent increase in $P\mathrm{tc}_{\mathrm{CO}_2}$, denoting respiratory depression associated with inhalation anaesthesia.

Transcutaneous electrodes provide a useful non-invasive method of monitoring respiratory function and it is suggested that their use in routine paediatric anaesthesia should be more fully evaluated.

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ELECTRICAL ACTIVITY OF CEREBRAL CORTEX DURING INDUCED HYPOTENSION IN MAN: A COMPARISON OF SODIUM NITROPRUSSIDE AND TRIMETAPHAN

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The electroencephalogram (EEG) and mean arterial pressure (MAP) were monitored directly in humans during induced hypotension in clinical practice The EEG and cerebral function monitor (CFM) were recorded using biparietal needle electrodes and the MAP using an intra-arterial cannula connected to a transducer. Twenty normotensive, fit adult patients received either trimetaphan (TMP) or sodium nitroprusside (SNP). The CFM traces were analysed according to mean, upper and lower levels (Prior, Maynard and Brierley, 1978). Anaesthesia comprised induction with thiopentone, intubation and controlled ventilation of the lungs to normocapnia with a mixture of nitrous oxide and oxygen with 0 5% halothane under neuromuscular blockade with tubocurarine.

Recording of CFM, EEG, MAP and end-tidal carbon dioxide concentration began during the normotensive period and continued until MAP returned to normal Hypotension was induced with either TMP to a maximum rate of 10 mg kg^{-1} h^{-1} or SNP to a maximum total dose of 1 5 mg kg^{-1}, selected randomly. Propranolol was used in 1-mg increments when the administration of either TMP or SNP had resulted in tachycardia. The aim of the study was to achieve a mean arterial pressure of 40 mm Hg, and to record CFM, EEG, MAP and end-tidal carbon dioxide at this level.

Reduction of MAP was quicker and greater with SNP Significant differences in EEG voltage between the two agents were seen in the range 55–40 mm Hg, electrical activity being better maintained with SNP. However, all patients showed some decline in EEG voltage with hypotension and half of these showed highly significant correlations with MAP. These pressure-dependent cerebral effects were not predictable in terms of age, preoperative arterial pressure, or hypotensive agent Our work supports previous experimental evidence that, during more profound hypotension, cerebral electrical activity is better maintained with SNP than with TMP (Stoyka and Schutz, 1975, Ishikawa and McDowall, 1981). The results indicate also that controlled hypotension should be accompanied by cerebral as well as arterial pressure monitoring if reductions in arterial pressure are to be more than modest. For this purpose, a simple measure of total EEG power or filtered EEG voltage envelope (CFM) is better than measurements of power distribution in different frequency bands.

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A COMPARISON OF NEUROMUSCULAR RECOVERY FOLLOWING BLOCKADE BY ATRACURIUM AND PANCURONIUM

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To test the clinical impression that the recovery of peripheral muscle power was quicker and more complete if atracurium rather than pancuronium had been used, 30 fit patients undergoing minor surgery, which did not affect the diaphragm, abdominal muscles or the dominant arm, were randomly allocated to two equal groups. All received temazepam 10 mg orally 1 h before surgery and anaesthesia was induced with fentanyl 2 $\mu g\ kg^{-1}$ and a sleep dose of thiopentone. One group (six females, nine males; mean age 41.2 yr, range 18–58 yr, mean weight 68.7 kg, range 45–95 kg) then received pancuronium 0.08 mg kg^{-1} and the other (seven females, eight males; mean age 30 yr, range 18–57 yr; mean weight 66.5 kg, range 49–81 kg) received atracurium 0.3 mg kg^{-1}. Maintenance was by ventilation to normocapnia with 33% oxygen and 67% nitrous oxide. Increments of fentanyl and myoneural blocker equal to a quarter of the initial doses were given when required.

Neuromuscular blockade was monitored by the train of four at intervals of not less than 12 s. Whenever surgery was complete, anaesthesia was continued until the third component of the train of four was just palpable to the observer. The residual block was then antagonized with neostigmine 2.5 mg and atropine 1.2 mg.

Before the premedication and at 30, 60, 90 and 120 min after reversal, each patient completed tests of muscle power. Grip strength was measured as the ability to compress a fixed volume of gas in a syringe (average of five attempts in 15 s). The maximum inspiratory force when inhaling from residual volume and the maximum expiratory force when exhaling from maximum lung volume (average of three attempts) were recorded on a Bourdon pressure gauge. The ability to head lift adequately for 5 s and the presence or absence of double vision was noted.

The results demonstrated that the recovery of grip strength and expiratory force were slower and less complete at up to 120 min after reversal from pancuronium ($P < 0.001$, Wilcoxon rank sum test). There was, however, no significant difference at 60 min and later between the two groups with respect to inspiratory force. The occurrence of double vision was more frequent in the pancuronium group and the 5-s head lift demonstrated no significant difference between the groups.

These findings confirm our original clinical impression that, following antagonism of neuromuscular blockade, recovery of the peripheral muscles is faster and more complete after atracurium than after pancuronium. In addition, it has emerged that the hand grip is a sensitive and easily performed test of the return of muscle power and that the 5-s head lift is an insensitive index of neuromuscular recovery.

LATENT AND MANIFEST ONSET CHARACTERISTICS AFTER ADMINISTERING PANCURONIUM, TUBOCURARINE OR A MIXTURE OF BOTH AGENTS

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Potentiation of neuromuscular blockade when mixtures of certain non-depolarizing agents are administered has been demonstrated *in vivo* (Wong, 1969) and *in vitro* (Pollard and Jones, 1983). This study was designed to investigate the speed of onset and onset characteristics of pancuronium, tubocurarine and a mixture of both agents.

Following approval by the hospital ethics committee, 24 ASA class I patients of both sexes were studied. Patients were allocated at random to one of three groups to receive tubocurarine 0.6 mg kg^{-1}, pancuronium 0.1 mg kg^{-1} or a mixture of these drugs (pancuronium 0.05 mg kg^{-1} plus tubocurarine 0.3 mg kg^{-1}). Anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen and additional increments of thiopentone as necessary. The ulnar nerve of the non-dominant arm was subjected to the train-of-four (TOF) pattern of stimulation at the wrist via surface electrodes and the evoked force of the adductor pollicis muscle was measured. After a control twitch had been recorded, the drugs were injected i.v. via a fast running infusion. All measurements were completed before surgery.

The time from injection to a 90% reduction in T1 was defined as the total onset time. The time from injection to the first clearly (>5%) reduced T1 was defined as the latent onset time, and the time from the first clearly reduced T1 to 90% T1 depression was defined as the manifest onset time. We also measured fractional onset times to 50% and 75% T1 depression. Results are shown in table I.

The three groups were comparable with respect to age, weight and pre-induction haemodynamic values. One patient was excluded from statistical analysis. Seven patients received tubocurarine, seven received pancuronium and nine received the mixture. During the onset of neuromuscular blockade, tubocurarine was associated with significantly more TOF fade at 75% T1 depression than was either pancuronium ($P < 0.05$) or the mixture ($P < 0.01$). In addition, T1 was significantly greater

TABLE I. *Onset times (min)*

	Tubocurarine	Pancuronium	Mixture
Latent	0.69 (0.32)	0.93 (0.56)	0.61 (0.14)
Manifest to			
50%	0.23 (0.18)	0.38 (0.31)	0.31 (0.20)
75%	0.89 (0.63)	0.72 (0.32)	0.72 (0.30)
90%	1.57 (0.94)	1.13 (0.54)	1.07 (0.37)
Total	2.25 (1.23)	2.07 (0.92)	1.67 (0.49)

when the fourth twitch (T4) disappeared following tubocurarine compared with pancuronium or the mixture ($P < 0.01$). The mixture had the shortest latent onset time and pancuronium the longest and most variable Thereafter, the mixture behaved in a manner almost identical to pancuronium, having very similar manifest onset times to 50%, 75% and 90% T1 depression. Tubocurarine, although having an initially rapid manifest onset time, subsequently showed a tailing off in speed of onset such that it had the slowest total onset time. The mixture had the most rapid total onset time and pancuronium was intermediate

In conclusion, we have shown that mixtures of drugs do not necessarily have onset characteristics which are simply a composite of the individual agents, and that the total onset time of neuromuscular blockade may be reduced by administering mixtures of drugs The latter observation may have clinical significance.

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THE EFFECT OF DILTIAZEM ON INTRACRANIAL PRESSURE IN CATS

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INTRACRANIAL PRESSURE CHANGES DURING INFUSIONS OF VERAPAMIL AS COMPARED WITH SODIUM NITROPRUSSIDE

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KETANSERIN AND POSTOPERATIVE HYPERTENSION FOLLOWING CARDIOPULMONARY BYPASS

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Postoperative hypertension occurs frequently following myocardial revascularization Plasma concentrations of potent vasopressors are known to be increased significantly following cardiopulmonary bypass (CPB) and during early recovery. Recent investigations implied that serotonin was an important aetiological factor in the pathophysiology of postoperative hypertension, as ketanserin, a new serotonin antagonist, was shown to decrease arterial pressure in patients developing hypertension after operation (Van der Starre et al., 1983). The following investigation aimed to study the antihypertensive mechanism of ketanserin, which is known also to possess alpha-adrenoceptor blocking properties, and serotonin concentration assayed as plasma 5-hydroxindoles (5-HI), and platelet 5-HT

We studied 13 patients, undergoing CPB for coronary artery bypass grafting. Blood samples for plasma 5-HI and plasma catecholamine concentrations were taken at intervals before, during and following CPB. During early recovery all patients had arterial pressures > 150/90 mm Hg and were given ketanserin 0.15 mg kg^{-1} followed by an infusion of 4–6 mg h^{-1}. A phenylephrine dose–response curve was obtained before and during infusion of ketanserin.

No significant changes in plasma 5-HI could be observed at any time. There was no correlation between systolic pressure and plasma 5-HI concentration Ketanserin decreased systolic and diastolic pressures in 11 patients, but failed to do so in two patients There was a significant shift of the phenylephrine dose–response curve to the right during infusion of ketanserin at one of three different phenylephrine doses. Adrenaline and noradrenaline plasma concentrations were markedly increased during early recovery, but did not change significantly over the 30-min observation period. The very high plasma concentrations of adrenaline and noradrenaline confirm the results of previous studies.

The arterial pressure-decreasing effect of ketanserin is in part a result of alpha-adrenoceptor blockade, but does not appear to be related to increased serotonin activity. Plasma serotonin concentration does not appear to be involved in the short term regulation of cardiovascular homeostasis during cardiopulmonary bypass (Anger and Prys-Roberts, 1984).

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EFFECTS OF ETHANOL ON PSYCHOMOTOR PERFORMANCE

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Ethanol is depressant to the central nervous system and its effects should be quantifiable with modern psychometric testing. The following study was performed using a battery of psychomotor tests which are considered to be useful in assessing central nervous system depressants, including many drugs used in anaesthesia

The study involved eight male volunteers who each received three doses of ethanol (0.2 g kg^{-1}, 0.4 g kg^{-1} and 0.8 g kg^{-1}) and a placebo on separate occasions. The study was randomized and double-blind, the taste of the alcohol being obscured to the extent that neither the alcohol or its dose could be differentiated from the placebo.

The battery of psychomotor tests included: choice reaction time (CRT); decision making time (DMT); continuous attention task (CAT); auditory vigilance (AVT), critical flicker frequency (CFF) and body sway (BS).

In addition, three visual analogue scales, the opposite ends of which were: bored/interested, steady/dizzy and alert/drowsy, were used. The subjects were tested at 0, 30, 60, 120, 150 and 180 min after swallowing the ethanol over 10 min on an empty stomach Blood samples for plasma ethanol concentrations were taken at 0, 10, 20, 30, 40, 50, 60, 75, 90, 120, 150 and 180 min after the beginning of ethanol ingestion.

The plasma concentrations showed a linear relationship with dose. At the highest dose all the subjects had reached or passed the legal limit for ethanol and driving (17.4 mmol litre^{-1} or 80 mg dl^{-1}). The peak values occurred 30–60 min after the beginning of intake.

Gross changes in psychomotor performance were not seen As expected, the highest dose was associated with the greatest change but this only reached statistical significance (using Friedman analysis) in the case of BS, CRT and CAT Moreover, these significant changes did not occur coincidentally with the peak ethanol concentrations, but 150 and 180 min after beginning ingestion The three visual analogue scales all showed significant differences with the highest dose. Interest and dizziness were increased during peak ethanol plasma concentration, as was drowsiness at 150 min Psychomotor performance decreased as the subjects became drowsy.

Ethanol, even at high doses, had only minor effects on the psychomotor tests used, which have been shown to be quite sensitive to other central nervous system depressants.

EVOKED POTENTIALS DURING ISOFLURANE ANAESTHESIA

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We have shown previously that nitrous oxide, in increasing concentrations up to 50%, produces a graded reduction in visual evoked potential (VEP) and somatosensory evoked potential (SEP) amplitudes. There were no alterations in brainstem latencies (BAER) (Sebel, Flynn and Ingram, 1984). We have now studied the effects of increasing concentrations of isoflurane on VEP, SEP and BAER

Eight unpremedicated healthy patients (four male, ages 50 9 ± 10.8 yr), scheduled for elective surgery, were studied. Anaesthesia was induced with a sleep dose of thiopentone, with vecuronium 6–8 mg for neuromuscular blockade. Following endotracheal intubation, the lungs were ventilated with isoflurane in oxygen using a Manley ventilator. Inspired isoflurane concentration was adjusted to maintain an end-tidal isoflurane concentration of 0.55% for 15 min and 1.1% for 15 min (approximately equivalent to 0 5 and 1 0MAC), measured using an Engstrom EMMA End-tidal carbon dioxide concentration was maintained at 4–5%. If time permitted, the isoflurane concentration was increased to 1.65% (1.5MAC) for 15 min (four patients). Evoked potentials were recorded before induction of anaesthesia and at the end of each 15-min period Standard electrode derivations were used. Stimulus parameters were: BAER, 10-Hz square wave clicks at 80 dB hearing level for 1024 repetitions, VEP, 2-Hz stroboscopic flash stimulation for 128 repetitions, SEP, 100-μs constant current pulse applied over the median nerve at 2 Hz for 256 repetitions. A Medelec Sensor and Apple microcomputer were used to compute and store the evoked potentials Linear regression was calculated for the waveform latencies and amplitudes against isoflurane concentrations. A *t* test was used to test the difference of the mean slopes from zero Data are presented as mean (± SD)

There were significant increases in onset latency of both SEP (slope 1.81 ms %$^{-1}$, (± 0.78), $P < 0.005$) and VEP (17.65 ms %$^{-1}$ (± 8 77), $P < 0.005$). SEP amplitude (–3 11 μV %$^{-1}$ (± 2 37), $P < 0.005$) and VEP amplitude (–7 53 μV %$^{-1}$ (± 4.7). $P < 0\ 005$) decreased with increasing concentrations of isoflurane. There were no consistent changes in latency of wave I of the BAER, but latencies of waves III (0.88 ms %$^{-1}$ (± 0 58), $P < 0.05$) and V (0.29 ms %$^{-1}$ (± 0 08) $P < 0.005$) increased

This study showed that isoflurane produced increased latencies of VEP, SEP and waves III and V of BAER and decreased amplitudes of VEP and SEP. This is in keeping with the effects of halothane and enflurane on BAER latencies (Thornton et al., 1984) and halothane on VEP latencies (Uhl et al., 1980) Changes in evoked potential latencies and amplitudes may therefore prove a useful indicator of depth of anaesthesia.

ACKNOWLEDGEMENT

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EFFECT OF ALTHESIN UPON SPONTANEOUS LOWER OESOPHAGEAL CONTRACTILITY (SLOC) IN MAN

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Spontaneous lower oesophageal contractility (SLOC), a stress-related tertiary activity of the human oesophagus, can be measured during "light" general anaesthesia, despite full skeletal muscle paralysis. SLOC is usually completely suppressed by volatile agents at an end-expired concentration of 2.0 MAC (Evans, Davies and Wise, 1984). The effects of increments of an i.v anaesthetic (Althesin, Glaxo) upon SLOC during nitrous oxide–oxygen anaesthesia in man have been examined.

Adult patients undergoing elective abdominal surgery were studied. The investigation was approved by the local ethics committee and informed consent was obtained

Anaesthesia was induced in unpremedicated patients with Althesin 0.05 ml kg^{-1} i.v. (following a test dose of 0.25 ml); alcuronium 0.3 mg kg^{-1} was also given. Tracheal intubation was performed and the lungs were ventilated with nitrous oxide and oxygen (50:50) by means of a non-rebreathing system Tidal volume was set to 10 ml kg^{-1} and the minute volume to 100 ml kg^{-1} min^{-1}.

The adequacy or depth of anaesthesia was judged by frequent measurement of clinical signs (systolic pressure, heart rate, sweating and tear formation). Increments of Althesin 0.02 ml kg^{-1} were given when, on the basis of clinical signs, the anaesthesia was judged to be "light".

Simultaneously SLOC was measured with a water-filled balloon-tipped catheter positioned 35 cm from the lips and connected to an external pressure transducer. The recordings of SLOC were made on a range of 0–100 mm Hg and to preclude bias were not visible to the clinician monitoring the patient and controlling anaesthetic supply.

Thirty-six top-up increments of Althesin were given to 12 patients The mean interval between increments was 17 min The chart recordings of SLOC were examined to provide a measure of the *rate* (contractions per minute) and the *amplitude* (mm Hg) of SLOC for each minute before and after the administration of the top-up increment. In order to exclude signals arising from IPPV and cardiac movement, pressure changes of less than 25 mm Hg were excluded from the analysis.

Changes in rate. before the top-up increment of Althesin, there was a progressive increase in SLOC rate to a peak of 3.7 contractions per minute which decreased to a low of 1.0 in the 3rd and 4th minutes after the top-up (fig. 1).

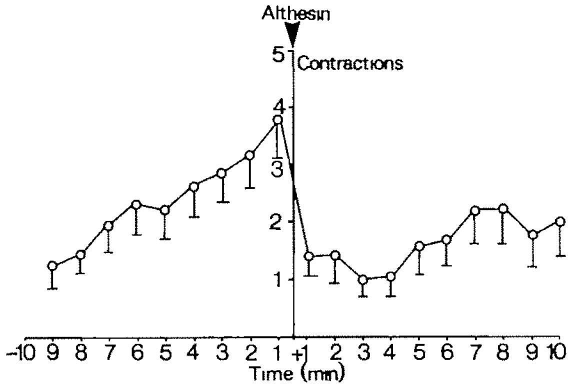

FIG 1. Changes in spontaneous lower oesophageal rate (number of contractions per minute) before and after Althesin

Changes in amplitude. no significant change was produced in the recorded SLOC amplitude after the incremental top-up.

Deepening anaesthesia with increments of Althesin results in a reduction of SLOC rate, but no change in SLOC amplitude. Although the analysis was confined to responses greater than 25 mm Hg, it appears that an individual SLOC response tends to be an "on–off" response, and not a graduated response; this contrasts with the graduated response observed in secondary provoked LOC (Evans, Davies and Wise, 1984).

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LIGNOCAINE CONCENTRATIONS AFTER 5% LIGNOCAINE OINTMENT TO THE TRACHEA

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Arterial plasma concentrations of lignocaine were studied in 12 patients following insertion of a tracheal tube the cuff area of which was smeared with 5% lignocaine ointment (Biorex Ltd, U K.) Two millilitre of ointment (114 mg) was used and arterial blood samples were taken every 5 min until 30 min and in eight of the patients at 40, 50, and 60 min after insertion and inflation of the tracheal tube and cuff.

Plasma lignocaine concentrations were determined using gas–liquid chromatography with cyproheptadine as internal standard (Tucker, 1970) Results are shown in figure 2

Mean and standard deviation of baseline values before any lignocaine were 0.3 ± 0.3 µg ml⁻¹, and are attributed to unknown cross-reacting substances At 5 min mean values of 1.8 ± 1.6 µg ml⁻¹ occurred and in one patient with liver disease,

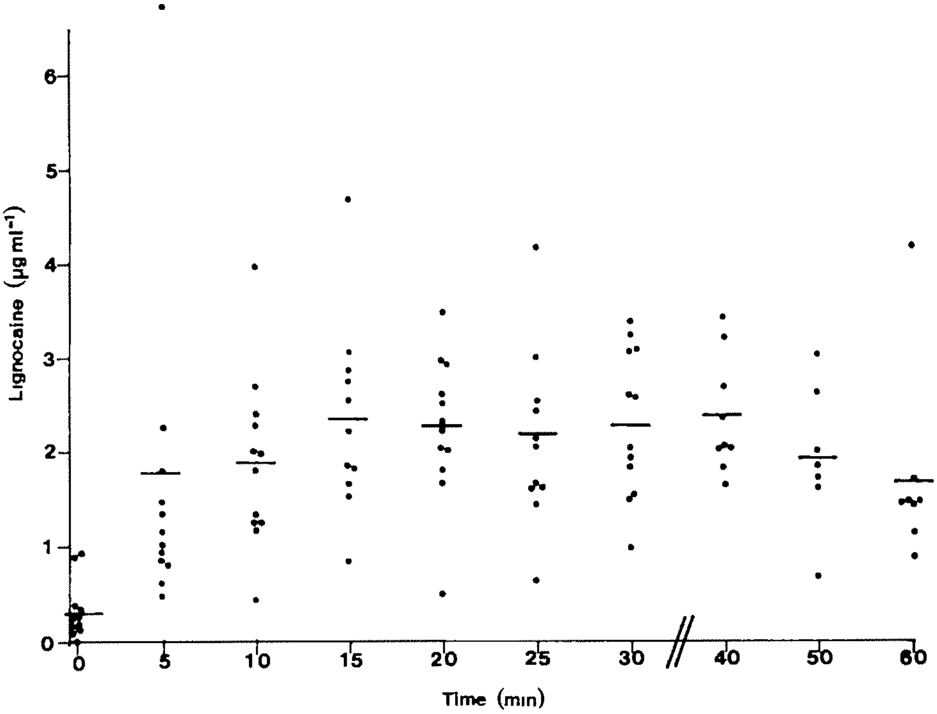

FIG 2. Arterial lignocaine concentrations after 5% lignocaine ointment 2 ml to the trachea

lignocaine 6.7 $\mu g\ ml^{-1}$ was found. At 10 min lignocaine concentrations were 1.9 ± 0.9 $\mu g\ ml^{-1}$; at 20 min they were 2.3 ± 0.8 $\mu g\ ml^{-1}$ and remained over 2.0 $\mu g\ ml^{-1}$ until 60 min, when a mean value of 1.7 ± 1.0 $\mu g\ ml^{-1}$ was obtained.

We were surprised to find high concentrations of lignocaine so early following tracheal ointment and to find that these persisted for at least 1 h after tracheal intubation.

Arterial plasma concentrations in children receiving 3 mg kg^{-1} of 20% lignocaine spray gave maximum values of 2.5 $\mu g\ ml^{-1}$ at 5 min and decreased slowly over 60 min to about 0.7 $\mu g\ ml^{-1}$ (Pelton, 1970).

After 4% lignocaine 2 mg kg^{-1} in adults, a mean value of 1.7 $\mu g\ ml^{-1}$ was found at 15 min in six patients. The addition of an unknown quantity of 2% viscous lignocaine to the tip of the endotracheal tube gave a value of 2.0 $\mu g\ ml^{-1}$ at 15 min in four patients (Viegas and Stoelting, 1975).

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BONE MARROW CHANGES AFTER CHRONIC INHALATION OF NITROUS OXIDE

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Inhalation of nitrous oxide (N_2O) inactivates vitamin B_{12} by oxidation, with impairment of DNA synthesis and the development of megaloblastic haemopoiesis. Bone marrow changes have been documented in patients who are exposed to N_2O over prolonged periods, or after multiple short term exposures (Laasen et al., 1956). Anaesthetists are chronically exposed to N_2O, but Nunn and colleagues (1982) failed to find any evidence of abnormality in the serum concentrations of methionine in 10 anaesthetists exposed to average concentrations of N_2O between 150 and 400 p.p.m., suggesting normal activity of the enzyme methionine synthetase, of which vitamin B_{12} is a co-factor. Dentists, however, are exposed to concentrations of up to 7000 p.p.m. and Layzer (1978) has reported neurological features similar to those occurring in subacute combined degeneration of the cord in 15 dentists who were exposed to nitrous oxide. For this reason we decided to investigate the potential toxic effects of N_2O in dentists.

Twenty-two dentists took part in the study which consisted of assessing the exposure of each subject to N_2O during normal working conditions. N_2O sampling was performed using a Nitrox N_2O dosimeter (Landauer Labs) attached to the lapel of each dentist, and the total exposure expressed as p.p.m. hours. A time-weighted average was then calculated. Only two of the subjects used scavenging, and this was shown to be ineffective.

Each subject was investigated by means of a questionnaire and a full neurological examination. Haematological investigations included a full blood count and measurement of serum B_{12} and folate concentrations. A bone marrow aspiration was performed in each patient and this was examined histologically, and by a deoxyuridine suppression test, which is a sensitive indicator of abnormality of vitamin B_{12} metabolism. In no subject was any neurological deficit detected and all measurements made on the peripheral blood were normal. In three subjects, however, an abnormal DU test was found and in two of these, polysegmented neutrophils, indicative of impaired DNA synthesis, were present.

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PLASMA METHIONINE CONCENTRATIONS DURING ELECTIVE SURGERY AND NITROUS OXIDE ANAESTHESIA

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Exposure to anaesthetic concentrations of nitrous oxide will inactivate vitamin B_{12} and inhibit the activity of methionine synthase, of which B_{12} is the bound co-factor. Plasma methionine concentration is reduced to 30% of the value before operation after 8 h exposure to nitrous oxide in man (Skacel et al., 1983) and reduced values have also been found in rodents after 24 h exposure (Lumb et al., 1983). However, there are no data relating to shorter durations, corresponding to the majority of routine surgery.

We have measured plasma methionine, tryptophan, phenylalanine and S-adenosyl methionine (SAM) concentrations before and after routine anaesthesia including nitrous oxide for durations of 25–217 min and compared the results with normal control subjects. Amino acids were measured by high pressure liquid chromatography, and SAM by the method of Baldessarini and Kopin (1966).

Concentrations of all three amino acids were significantly lower in the preoperative samples than in the samples from the control subjects. The mean methionine concentration was 22.6 mmol $litre^{-1}$ in the controls and 14.8 in the patients before induction ($P < 0.001$). There was no significant difference in SAM concentrations. Values for methionine, phenylalanine and SAM at the end of operation were not significantly different from those at induction (mean duration 85 min). There was a small although significant reduction in tryptophan. For individual patients there was no correlation between the change in methionine concentration and the duration of exposure to nitrous oxide.

Turnover of methionine is of the order of 60 mmol day^{-1}, of which 10 mmol is contained in the diet, 40 mmol is the balance between catabolism and protein synthesis and only 5 mmol is used by the transmethylation reaction catalysed by methionine synthase. The present study showed that preoperative starvation is a major factor affecting methionine (and other amino acid) concentrations. However, catabolism is likely to be increased by surgery, and this may explain the lack of response to exposure to nitrous oxide for the duration we have studied.

Although it seems clear that typical exposures to nitrous oxide for routine surgery have no effect on plasma methionine concentrations, it remains to determine the time course of changes between 3 and 8 h, when concentrations are known to be reduced, and to determine whether changes occur in the early period after operation, since the recovery of full methionine synthase activity is known to take several days.

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QUALITY OF BLOOD PREPARED WITH A CELL SAVER

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Compelling reasons to avoid donor blood include immune reactions, risk of infection and physical hazards associated with hyperkalaemia and donor red cells which are depeleted of 2–3, diphosphoglycerate (2–3, DPG).

Autotransfusion avoids many of these problems and has been shown to decrease the need for donor blood (Cosgrove et al., 1978). However the quality of this blood varies greatly.

In an effort to determine the quality of blood prepared by the Dideco Autotrans BT 795 cell saver, we studied 40 patients having cardiac surgery. In 20 patients (group I) the cell saver was used during operation and at the end of cardiopulmonary bypass blood which remained in the pump was also passed to the cell saver for processing. Following centrifugation and washing, the saved blood was sampled from the reinfusion bag before transfusion. Sampling was done in group II on the first donor blood pack used (mean age 4.5 days).

Comparisons included haemoglobin and 2–3, DPG concentrations, white cell counts and lysozyme concentrations, pH and potassium concentrations and blood films. Heparin concentrations were measured on cell saved blood.

Results showed that the cell saver yielded blood with a high haemoglobin and normal 2–3, DPG concentrations. Worrying features about it included the high white cell counts, many of which were damaged, and high concentrations of lysozyme. Heparin concentrations were higher than recommended values.

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CHANGES IN PLASMA BETA-ENDORPHIN WITH VARIOUS ANAESTHETICS

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Beta-endorphin is an endogenous polypeptide with analgesic properties and a role in the perception of pain. Plasma beta-endorphin concentrations increase in response to the stress of surgery and it has been suggested that beta-endorphin may mediate analgesia during general anaesthesia. The purpose of this study was to measure and compare the changes in the concentration of plasma beta-endorphin in patients managed by various anaesthetic techniques during abdominal surgery

Thirty adults in physical status I–III were separated into three groups to receive nitrous oxide, oxygen and tubocurarine (group A), nitrous oxide, oxygen with enflurane (group B), or nitrous oxide, oxygen with isoflurane (group C). No patients received opioids before surgery. Premedication doses of promethazine and hyoscine were adjusted for age and weight. Thiamylal sodium 1–4 mg kg^{-1} was used for induction before the inhalation agent(s) In group A maintenance was provided by 70% nitrous oxide in oxygen, with tubocurarine for intubation and further increments for paralysis as needed. In groups B and C suxamethonium was used to facilitate intubation and maintenance was with enflurane or isoflurane vapour, respectively, in 50–70% nitrous oxide in oxygen. Peripheral venous blood samples were drawn at specified times: before, during and after anaesthesia and surgery. The collected plasma was frozen until time of assay. Radioimmunoassay was carried out using a kit from the Immuno Nuclear Corporation which has less than a 5% crossreactivity with beta-lipotropin and detects a range of beta-endorphin 10 4–276.8 pg ml^{-1}. All samples from each patient were initially run on the same assay. Results above the upper limit of sensitivity were obtained by dilution on a subsequent re-run

The measurements of plasma beta-endorphin are presented in table II.

Increases in beta-endorphin have been consistently associated with surgical stress rather than anaesthesia. In our study, beta-endorphin was increased after induction of anaesthesia in all groups, but most markedly in group A. There were subsequent increases in all three groups following surgical stimulation and high concentrations were found consistently in both recovery room samples in all groups, with group A being highest The higher concentrations of plasma beta-endorphin in group A may reflect the lighter anaesthesia provided by nitrous oxide alone.

TABLE II. *Plasma beta-endorphin responses (pg ml^{-1}) to anaesthesia and surgery NB=Night before; PA=preinduction; PIND=30 min after induction, before surgical incision; PINC=30 min after incision; RU1=30 min after anaesthesia in recovery, RU2=60 min after anaesthesia in recovery. Mean values ± SEM Group* n=*10*

Blood Sample	Group A	Group B	Group C
NB	23.08± 3.2	20.7± 5.5	28 2± 3.5
PA	28.76± 4.4	22.1± 1.9	30 7±20.1
PIND	141.63± 45.4	53.5±14.3	58 9± 4.4
PINC	375.63± 86.2	157.2±40.9	196 2±56.8
RU1	324 32±125.3	175.6±32.8	162.5±35.3
RU2	303.14± 89.6	187.8±33.4	212 3±48.5

DIRECT MEASUREMENT OF INTRA-OCULAR PRESSURE IN DOGS DURING NEUROMUSCULAR BLOCKADE WITH METOCURINE, PANCURONIUM, ATRACURIUM AND VECURONIUM

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This study was undertaken to assess the effects of the neuromuscular blocking agents atracurium, vecuronium, pancuronium and metocurine, on the intra-ocular pressure of dogs

The study was peformed on five conditioned, mature male foxhounds. The dogs underwent tracheal intubation immediately after induction of anaesthesia with thiopentone 10 mg kg^{-1} and were ventilated with 67% nitrous oxide in oxygen Ventilation was controlled to maintain an end-tidal PCO_2 of 5 kPa, and anaesthesia was maintained with an infusion of fentanyl 5-10 $\mu g\ kg^{-1}\ h^{-1}$. Direct and continuous measurements were taken of arterial pressure, central venous pressure and intra-ocular pressure, the last via a 22-gauge needle inserted to the anterior chamber of the eye A force displacement transducer was attached to the hind paw to monitor muscle twitch following supramaximal stimulus of the nerve to gastrocnemius. These four measurements were displayed on a four-channel polygraph Control values were obtained and atracurium 0.4 mg kg^{-1}, vecuronium 0.1 mg kg^{-1}, pancuronium 0.1 mg kg^{-1} or metocurine 0.3 mg kg^{-1} were given in a randomized fashion and on different days, although up to two agents were given on each day Measurements of HR, MAP, CVP, and IOP were noted at 2, 5, 10, 20 and 30 min after giving the neuromuscular blocking agent. Blood-gas estimations were undertaken before blockade and at intervals 5, 10, 20 and 30 min after injection of the agents

The results as displayed on the polygraph indicated that the least effect on IOP and cardiovascular state followed neuromuscular blockade with vecuronium and atracurium However, statistical analysis of the data on MAP, CVP, and IOP taken as a percentage change from control, showed no significant differences between groups at any time. The heart rate was significantly greater at the 2-min observation in the pancuronium group

THE INTERACTION OF ATRACURIUM AND VECURONIUM

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The neuromuscular blocking actions of atracurium and vecuronium acting separately and in combination have been compared using the evoked EMG of the adductor pollicis muscle in 98 patients, status ASA I or II.

Dose–response curves have been drawn for the drugs given separately and found to be non-parallel ($P < 0.05$) The equations for the best-fit straight lines were for atracurium: $R = -145.9 - 102.1 \ln D$, and for vecuronium: $R = -183.2 - 64.9 \ln D$, where R = % response and D = dose. Atracurium was calculated to be 5.25 and 4.1 times less potent than vecuronium, ED_{50} and ED_{95} respectively.

The effect on neuromuscular transmission of a combined medication using equipotent doses of atracurium and vecuronium, determined from the dose–response plots, was found to be greater than would be expected by addition of their separate actions. The combination of small doses resulted in significant neuromuscular blockade.

SINGLE BOLUS DOSE *V* CUMULATIVE DOSE TECHNIQUES FOR DETERMINING POTENCY OF ATRACURIUM

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The potency of a relatively short acting drug, such as vecuronium, has been shown to be greater when a single bolus dose method is used, in contrast to a cumulative dose method (Fisher et al , 1982), while no difference had been shown in case of pancuronium and tubocurarine (Donlon et al., 1980) Atracurium has a profile of action similar to that of vecuronium (Katz et al., 1982) Although Katz and others (1982) showed that a given dose of atracurium produced a greater degree of block when administered as a single bolus rather than in increments, there is no information about the comparative potency of the drug with the two techniques. This has been determined in the present study

Forty adult patients were premedicated with oral diazepam and anaesthetized with thiopentone, nitrous oxide in oxygen and increments of fentanyl and thiopentone. The contraction of adductor pollicis was recorded following stimulation of the ulnar nerve at the wrist with supramaximal stimuli at 0.1 Hz

Patients were allocated randomly to receive atracurium either as a single bolus dose (n = 30) or in an incremental (cumulative) fashion (n = 10). Those receiving the drug in a single bolus dose were further randomly allocated to receive 50, 100, 150, 200 or 250 $\mu g\ kg^{-1}$ The maximal reduction in the twitch height in these patients was recorded. In those receiving the drug in an incremental way, atracurium 50 $\mu g\ kg^{-1}$ was administered every time the twitch height was the same in response to three consecutive stimuli, until the twitch height was reduced by 95% or more Dose–response curves were constructed from the percentage twitch height reduction in each group.

The dose–response curves did not differ in their gradients, but that obtained with the single bolus dose technique was to the left of the one obtained with the cumulative dose technique. The ED_{50} and ED_{95} (table III) were both significantly lower with the single bolus dose technique ($P < 0.05$), showing atracurium to be apparently more potent using this method of assessment. This may be a more valid way of assessing the potency of relatively short acting drugs like atracurium, since most anaesthetists use such drugs as a bolus

TABLE III *Comparison of single bolus dose and cumulative dose methods (95% confidence limits)* *$P < 0.01$

	Single bolus dose method	Cumulative dose method
ED_{50} ($\mu g\ kg^{-1}$)	126* (115–137)	162 (149–175)
ED_{95} ($\mu g\ kg^{-1}$)	226* (207–246)	305 (275–336)

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PHARMACOKINETICS OF LAUDANOSINE AND QUATERNARY ALCOHOL AFTER AN I.V. BOLUS DOSE OF ATRACURIUM IN PATIENTS WITH IMPAIRED RENAL FUNCTION

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Atracurium is removed from the body by the Hofmann reaction, giving it a terminal half-life of about 20 min dependent on pH and temperature, but essentially independent of renal or hepatic function The breakdown products which still contain a quaternary nitrogen will be eliminated similarly, whereas other products may depend upon renal or hepatic integrity The present study was undertaken to compare the pharmacokinetics of some of these metabolites in patients with normal or impaired renal function.

Eight patients gave informed consent. Group I ($n = 4$) were ASA I undergoing minor gynaecological surgery. Group II ($n = 4$) were in chronic renal failure undergoing minor surgical procedures. Each patient was given an oral benzodiazepine premedicant and anaesthesia was induced with thiopentone 5–7.5 mg kg^{-1}. A bolus dose of atracurium 0.3–0.4 mg kg^{-1} was administered and ventilation controlled to normocapnia and physiological pH with 66% nitrous oxide in oxygen and 0.6% enflurane. After surgery all patients were allowed to recover spontaneously.

Before dosing and at regular intervals up to 500 min thereafter, blood samples were drawn from a peripheral vein and the plasma separated rapidly, acidified and frozen to –20 °C. An improved HPLC method allowed atracurium and less polar metabolites to be measured in a single 20-min analysis. The sensitivity limit for atracurium, laudanosine, the monoquaternary alcohol, tetrahydropapavarine, monoquaternary acid and mono-acrylate was about 10 ng ml^{-1} with fluorescence detection.

Concentrations of atracurium were found to be as expected from the doses given, except that group II concentrations were more variable than group I. Concentrations of products not mentioned further were never higher than 15 ng ml^{-1}.

The laudanosine and monoquaternary alcohol concentrations were analysed by non-linear least squares fitting to determine terminal half-lives (min) and apparent clearances (ml min^{-1} kg^{-1}) where Cl_{appar} = atracurium dose/area under metabolite concentration–time curve.

The results are shown in table IV as means ± standard deviations

TABLE IV. *Half-lives (min) and apparent clearances (Cl_{appar}) (ml min^{-1} kg^{-1}) of laudanosine and alcohol †n = 3; otherwise n = 4. ‡P < 0.05*

	Laudanosine		Alcohol	
	Half-life	Cl_{appar}	Half-life	Cl_{appar}
Group I	197±38	10±1	26±4	14±3
t test‡	ns	ns	ns	ns
Group II	266±83	9±7	31±8†	14±7†

This study suggests there are no significant differences between normal patients and those with renal failure in respect of half-lives or clearances of two of the metabolites of atracurium, although the variance of apparent laudanosine clearance is significantly greater ($F = 132, P < 0.01$) in renal impairment

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ATRACURIUM AND VECURONIUM CAUSE APNOEA AND LOSS OF KNEE JERK REFLEX BEFORE NEUROMUSCULAR BLOCK IN THE HAND IS COMPLETE

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Initial reports of hypopnoea preceding complete neuromuscular block in the hand (Norman, Read and duBoulay, 1980) have been confirmed for vecuronium and pancuronium in a previous study in 105 patients (Bencini and Newton, 1984) All these patients stopped breathing before the block in the hand was complete, and considerably before ideal paralysis for tracheal intubation was present That patients were able to buck and cough with considerably force suggests that voluntary neuromuscular function was present to a considerable extent in patients who were not breathing spontaneously.

To investigate this phenomenon further, 14 patients were monitored during routine induction of anaesthesia with thiopentone and nitrous oxide in the manner described previously Atracurium 0.5 mg kg^{-1} (seven) or vecuronium 0.1 mg kg^{-1} (seven) was given in a single bolus for neuromuscular blockade and intubation. In addition to the adductor pollicis single twitch response, the capnogram and pneumotachogram were recorded continuously, and the knee jerk was elicited regularly in time with the nerve stimulator (0.1 Hz). Manual ventilation was started after apnoea and maintained until the neuromuscular block in the hand was complete, when the trachea was intubated and the lungs ventilated In this way, the end-tidal carbon dioxide concentration was kept constant and within normal limits

All the patients stopped breathing and were areflexic before the neuromuscular block in the hand was complete Before 50% depression of twitch height, with vecuronium areflexia occurred in all and apnoea in six patients, and with atracurium apnoea occurred in all and areflexia in six. The sequence of events is summarized in table V

In an additional five patients receiving the same anaesthesia but no neuromuscular blocking agents, the knee jerk reflex remained intact for at least 5 min after the resumption of stable respiration following induction.

Waud and Waud (1972) showed that respiration can occur at deep levels of skeletal neuromuscular block. However, the patients in this study were neither blocked nor breathed, and the

TABLE V. *Summary of results Mean (SEM) time (s)*

	Atracurium	Vecuronium
Number	7	7
Time to.		
Start of hypopnoea	40.0 (3.6)	34.6 (4.7)
Twitch depression onset	55.7 (6.7)	48.6 (5.5)
Apnoea	63.6 (8.0)	61.7 (7.0)
Loss of knee jerk	64.3 (13.8)	59.3 (7.0)
50% twitch depression	115.6 (19.7)	85.7 (9.2)
Maximal twitch depression	226.0 (21.8)	176.0 (22.6)

loss of stretch reflex in the legs at the same time may suggest that the apnoea occurs through loss of intercostal stretch reflexes, there being no time for a build-up of carbon dioxide to restart respiration. The results demonstrate no significant difference between atracurium and vecuronium

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EFFECT OF SLEEP DEPRIVATION ON CHOICE REACTION TIME

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It is known that loss of sleep can affect task performance to a degree dependent on the task imposed (Glenville, 1978) To be sensitive, tests of performance should be boring and of long duration (Lisper and Kjellberg, 1972), but reduced subject compliance limits these features in practice

A new interactive computer program has been developed to test logical decision-making after periods of sleep loss. Following an initial introduction and familiarization, a test sequence is started. A set of six independent physiological variables (heart rate, arterial pressure, haemoglobin concentration, and serum sodium, potassium and urea concentrations), intended to represent the profile of a hypothetical patient, appear on screen for a limited period. Twenty sets are presented in each test. Subjects are instructed to accept or reject each set of variables on the basis of "normality", reference limits for each variable having been displayed in the program instructions. As a "reject" response can be made after reading only the top variable if this is outside the set limits, choice reaction time (ms) is recorded as the mean response time of "accept" decisions, since these require the evaluation of all the variables displayed Reaction time and accuracy are recorded onto disc after each test.

Registrar anaesthetists at Leicester Royal Infirmary were studied after their 24-h "on call" periods. Before testing, all subjects were given 8 weeks familiarization consisting of free access to the program. Initially, it was found that there was a trend of continuing improvement in performance, indicating an effect of learning. However, a consistent level of response with 100% accuracy was obtained in each individual subject after a minimum of 20 practice runs, following which testing began. Testing was carried out at 09.00 h under identical conditions, subjects being awakened at 08.30 h (if not awake already) and allowed their habitual caffeine or nicotine, or both. A record of the previous 24-h period activity was kept in a "log" from which duration of sleep was noted.

Initial results have been obtained in three subjects after 15 runs Although accuracy was maintained above 95% in all situations, a non-linear correlation between reaction time and sleep (expressed as a fraction of each individual's normal sleep time) was observed and a significant correlation between log [reaction time] and sleep was obtained ($P < 0.05$).

The program described may prove of value in studies on the effects of sleep loss on decision-making by medical staff if early results are confirmed.

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AN INVESTIGATION INTO THE SOURCES OF VARIABILITY IN PAIN DATA

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The study of most scientific subjects requires both accurate, repeatable measurements and a means of calibrating the scales on which these measurements are made. This has been a problem in pain research for many years There is a large amount of variabity in pain data and this study was designed to investigate some of the sources of this variability

Twenty healthy volunteers (10 male) aged between 18 and 25 yr, were given a series of randomized, standardized painful stimuli under controlled conditions in a distraction-free environment Each subject attended for a control session, followed by a treatment session in which either buprenorphine 0.4 mg or a matched placebo was given in a randomized, double-blind manner.

The stimuli consisted of 20 pressure stimuli, each lasting 10 s, applied to the tibia with a Salter algometer The subjects recorded their responses to the pain on a 10-cm visual linear analogue Differences between individuals and between the sexes were examined as sources of variation.

A series of multiple linear regressions was performed within a generalized linear interactive modelling program.

Transforming the data was found to have the greatest effect in reducing the variability of the data However, there was no obvious difference between Hill, arc–sine and log–log transformations

Differences between individuals were the next greatest source of variability in the data Sex also accounted for some of the variability, but considerably less than the two previous effects.

In conclusion, to minimize variability, pain data from visual linear analogues should be transformed, individuals should be used as their own controls if possible, and groups should be balanced for sex

AN OPEN COMPARISON OF PATIENT-CONTROLLED ON-DEMAND FENTANYL DELIVERED EITHER EXTRADURALLY OR I.V

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The morbidity associated with severe postoperative pain is well known. Because of this, techniques are constantly under investigation to improve the efficacy and safety of postoperative analgesia. Two separate avenues of work have been found to offer rich rewards in this field The first was the use of spinal and extradural opioids, whilst the second was the development of patient-controlled "on demand" analgesic systems

The author has reported previously on the use of thoracic extradural fentanyl for pain relief after operation (Welchew and Thornton, 1982) when it was found to be more effective than a conventional i m. regimen He has also shown, in a separate trial, that the optimal concentration for extradural fentanyl was

TABLE VI. *Doses of fentanyl received in each group*

	Mean	SD	Range
Extradural	44.0 $\mu g\,h^{-1}$	14.92	20–130 $\mu g\,h^{-1}$
I.v.	98.17 $\mu g\,h^{-1}$	51.28	10–290 $\mu g\,h^{-1}$

10 $\mu g\,ml^{-1}$ (Welchew, 1983). The trial reported here was designed to investigate the variability of dosing patterns in patients using patient-controlled on-demand extradural fentanyl. Twenty patients used a Janssen's Scientific Instruments On Demand Analgesic Computer (ODAC) to give themselves small incremental doses of fentanyl solution 10 $\mu g\,ml^{-1}$ after operation for 24 h. They were allocated randomly to two equal groups, the first of which had the drug delivered via a thoracic extradural catheter, whilst the other group had it delivered i.v. The two groups were not significantly different with respect to their ages and weights.

The results showed that the quality of analgesia in the two groups was very similar for most of the 24-h period of study, but was sigficantly better in the extradural group during 3 h of that time. Sedation scores were not significantly different in the two groups at any time, but nausea scores were, with significantly greater nausea in the i.v. group during the first 12 h of study. The doses of fentanyl consumed in each group are shown in table VI.

These illustrate that fentanyl consumption was much lower and less variable when the drug was delivered extradurally, compared with the i.v. route.

ACKNOWLEDGEMENTS

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SUSTAINED RELEASE ORAL MORPHINE IN CARDIAC SURGERY

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A benzodiazepine premedication followed by non-narcotic balanced general anaesthesia plus intrathecal morphine, given after induction of anaesthesia is a popular method of anaesthesia for cardiac surgery. The latter contributes to analgesia during operation and provides excellent prolonged analgesia after operation. However, its administration exposes patients to the risk of meningitis, spinal headache, nausea, vomiting, pruritus, urinary dysfunction and early and late respiratory depression (Bullingham, McQuay and Moore, 1982). The advent of sustained release oral morphine tablets (MST Continus) which have been shown to provide analgesia after surgery (Fell, Chmielewski and Smith, 1982) and which avoid many of the problems of spinal morphine, prompted this study. The aims were to compare sustained release oral morphine and lorazepam as premedicants and as respiratory depressants, and to compare postoperative pain scores and analgesic needs in patients receiving sustained release oral morphine and those receiving intrathecal morphine.

Thirty patients undergoing cardiac surgery were studied: 15 received sustained release oral morphine 100 mg plus metoclopramide 10 mg 2 h before operation; 15 received lorazepam 4 mg 2 h before operation and intrathecal morphine 1.25–2.0 mg following induction of anaesthesia. General anaesthesia in both groups was similar and consisted of otherwise non-narcotic balanced techniques.

Following premedication, arterial blood samples were compared every 15 min for 2 h. Sedation scores and anxiety levels were compared in the induction room. Postoperative linear analogue pain scores and analgesic requirements were compared.

Blood-gas analyses revealed slight but significant increases in Pa_{CO_2} caused by both premedicants. This occurred earlier and was more pronounced in patients who had received lorazepam. Sedation scores and anxiety levels were similar in both groups of patients. Pain scores after operation were significantly lower in patients who had received intrathecal morphine, and analgesic needs were also lower in this group.

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COMPUTER CONTROLLED INFUSION IN THE ASSESSMENT OF PHARMACOKINETIC PARAMETERS FOR ALFENTANIL

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An infusion regimen for alfentanil was devised to produce a constant plasma concentration using the two-compartment kinetic parameters of Bower and Hull (1982). The infusion rate is a summation of two components, a constant rate and an exponentially diminishing rate (Vaughan and Tucker, 1976). To simplify implementation, the exponentially changing rate was approximated into 10 changes until the constant infusion rate was reached. These infusion rates were calculated and controlled by means of an Apple II computer interfaced with an Imed 929 vol-

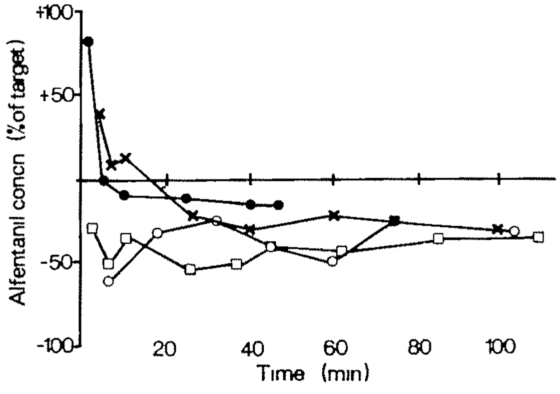

FIG 3. Mean plasma concentrations of alfentanil compared with target values.

umetric pump. The program contained the kinetic parameters and required operator input of patient body weight, concentration of alfentanil infusion, and target plasma concentration

In order to test the applicability of bolus derived kinetic parameters to infusion techniques, alfentanil was administered to four patients, using the computer system. Plasma concentrations were measured using radioimmunoassay (Bower and Hull, 1982) and mean values were found to be 22% lower than target concentration (fig. 3).

The infusion program was then modified by increasing the volume of the central compartment by 22% A second group of four patients was studied using this modified model, over periods ranging from 81 to 240 min. The mean plasma concentrations of alfentanil in the second group were in the range 70–90% above target concentration throughout the period of infusion

Computer controlled infusion provides a potentially useful tool for testing the validity of bolus-derived kinetic data. A third group of patients will be studied after further revision of the kinetic model.

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BODY SHAPE CHANGES ON INDUCTION OF ANAESTHESIA

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The surveying technique of stereophotogrammetry was used to investigate body shape change on induction of anaesthesia, to elucidate the decrease in lung volume (FRC) that occurs (Don, 1977). Two highly accurate plate cameras, fixed 560 mm apart (Officine Galileo A-Special), were suspended 1.6 m above patients on an operating table The patients lay on a mattress filled with plastic beads that could be made rigid by suction (VAC-PAC, Howmedica) to prevent body frame movement The phases of breathing were assessed by inspection and by monitoring intragastric pressure with a nasogastric tube A pair of photographs were taken at end-expiration, before and again immediately after induction of anaesthesia with i.v thiopentone 2–4 mg kg^{-1} The resulting pairs of photographs were set up in a stereoplotter (Wild A8) to generate contour diagrams of the visible portions of the body surface (fig. 4), and the volume of these parts calculated using a trapezoidal method Measurements were made between the sternal notch and the pubic arch and this distance was halved to yield arbitrary ribcage and abdominal portions

Initial results are available for five patients presenting for elective surgery. Induction of anaesthesia was associated with a mean decrease in the measured volume of 1 55% which was not statistically significant, nor sufficient to account for the expected decrease in FRC. However, there was a highly significant relationship between the change in volume and the degree of obesity of the patient (expressed as weight/ideal weight ratio) ($r = -0.86$). This was a result of a change in ribcage volume (volume before/volume after = 1.25 × −0.26 (body weight/ideal weight), $r = -0.95$).

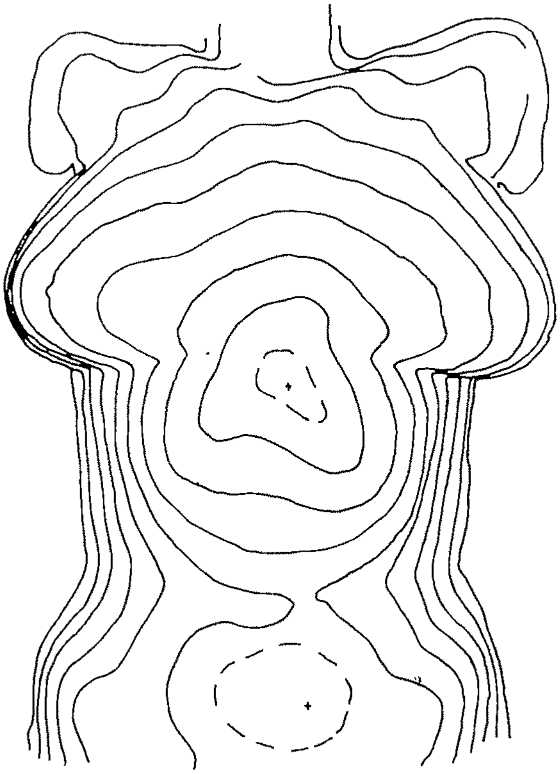

FIG 4. 10-mm contour plot of body surface before anaesthesia.

Our preliminary conclusion is that, in overweight patients, inspiratory ribcage activity is abolished on induction of anaesthesia and this could account for the increase in abdominal pressure seen in such subjects when anaesthesia is induced (Drummond and Park, 1984)

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MOVEMENT OF THE DIAPHRAGM ON INDUCTION OF ANAESTHESIA

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Since the study of Froese and Bryan (1974) it has been accepted that induction of anaesthesia in supine subjects is associated with a cephalad movement of the dependent part of the diaphragm, and that this movement could account for the decrease in FRC that occurs on induction of anaesthesia. However, quantitative data were only presented for two subjects, and since other studies suggest that the resting position of the diaphragm may not in fact alter on induction of anaesthesia, we studied 20 subjects before elective surgery by means of ultrasonic imaging.

A 3.5-MHz real time scanner was used to obtain an image of the

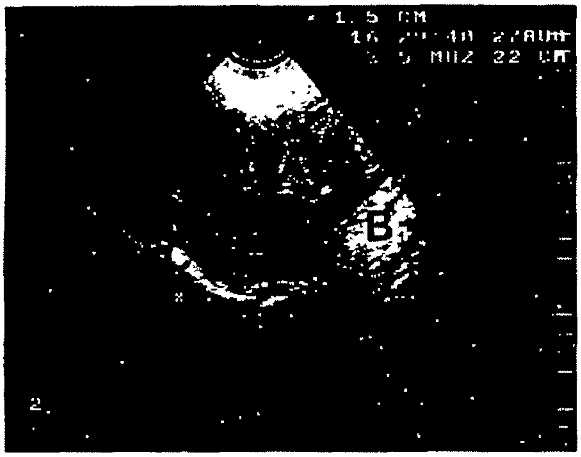

FIG 5 Sagittal ultrasonic image of diaphragm showing cursor position and direction of measurement of diaphragmatic excursion A: porta hepatis; B: perirenal fat; C. diaphragm

right hemidiaphragm in the sagittal plane. A section of the diaphragm showing the most movement during quiet breathing was identified and a cursor placed on this in the end-expiratory position (fig. 5) The movement of this sector was measured during quiet breathing, in the direction of the radius of curvature Anaesthesia was induced with thiopentone 2–4 mg kg^{-1} i.v. and the change in end-tidal position after induction of anaesthesia was measured.

Subjects ranged in age from 18 to 70 yr, height from 152 to 188 cm, and weight from 52 to 92 kg (71–130% expected weight) The mean excursion during quiet tidal breathing was 1.5 cm ± 0.5 (SD) This is similar to the value found by Wade (1954) using fluoroscopy

The mean change in position after induction of anaesthesia was 0.4 ± 0.5 cm. In 10 of the 20 subjects, the diaphragm moved cephalad (mean 0.8, range 0.4–1.4 cm). In eight, no movement was seen and in two a caudad movement occurred The pattern of movement was not related to age, sex or obesity The movements we observed were not sufficient to account for the FRC change that occurs with induction of anaesthesia.

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EFFECT OF AGE ON "INDUCTION DOSE" OF PROPOFOL

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There is an increasing awareness of the variability of response to drugs in the elderly which is particularly important with i.v. agents We report here a study of induction dosage of the emulsion formulation of 2,6, diisopropyl phenol (propofol) in fit unpremedicated patients aged 16–80 yr. The method of study was similar to that used for the assessment of factors influencing the onset time for thiopentone (Dundee et al., 1982)

TABLE VII. *Mean age, weight and onset time (±SEM) in patients given propofol at the height of forearm reactive hyperaemia*

Dose (mg kg^{-1})	2.0	2.5
n	10	14
Age (yr)	39±4.5	28±2.6
Weight (kg)	63±1.9	58±2.1
Onset of anaesthesia (s)	10.9±0.56	11.3±0.56

As this method is applicable only to drugs which in adequate doses induce sleep in one arm–brain circulation time, it was first necessary to show that this applied to propofol In a preliminary study carried out in 24 unpremedicated patients, bolus doses were given at the height of forearm reactive hyperaemia following arterial occlusion by tourniquet and the end-point taken as cessation of counting

The times in table VII are similar to those with the Cremophor formulation (Briggs et al., 1981) and with those for thiopentone, methohexitone and etomidate

In the definitive study, 214 consenting patients undergoing elective surgery, received an initial dose of propofol 1.25 mg kg^{-1} given over 20 s into a large forearm vein, followed by 10 mg every 15 s until loss of verbal contact occurred The dose was noted and anaesthesia continued with conventional agents

Patients were divided into 10-yr age groups with a minimum of 25 in each group We found a reduction in "induction dose" requirements with increasing age which became clinically obvious at 60 yr, the dose for patients younger than this averaged 1.99 ± 0.03 mg kg^{-1}, while that for patients older than 60 yr averaged 1.61 ± 0.03 mg kg^{-1}, the difference between these being significant ($P < 0.001$).

No explanation is offered for this phenomenon, but on the basis of this study, one would recommend caution with the dose of propofol in the elderly

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INCREMENTAL PROPOFOL FOR SHORT PROCEDURES

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The i.v. induction agent, propofol (2,6 diisopropyl phenol), was first introduced with Cremophor EL as the solvent It has now been reformulated as an emulsion in soya bean oil. The preparation containing Cremophor EL was shown to be a rapidly acting agent producing anaesthesia of short duration and without excitatory side effects (Briggs et al., 1981) These characteristics prompted us to investigate the use of the new propofol formulation in an incremental i.v technique for minor gynaecological procedures, using three different premedication regimens

One hundred and thirty-four fit women aged between 16 and 70 yr, and due to undergo dilatation and curettage or termination of pregnancy, were randomly allocated to three premedication groups Group 1 received lorazepam 1 mg 2 h before operation, group 2 received papaveretum 10 mg and hyoscine 0.2 mg 1 h before surgery; group 3 were not premedicated. Following a bolus of alfentanil 250 μg, anaesthesia was induced with propofol, containing 0.5% lignocaine to prevent pain on injection. This was given at a standard rate (9.5 mg every 10 s) to a standard end-point (loss of lash reflex + 1 ml) After induction, patients breathed 60% nitrous oxide in oxygen until the end of cervical dilatation, thereafter breathing 100% oxygen. Anaesthesia was maintained by incremental doses of propofol. Recovery time was assessed as the interval between the last incremental dose and the mean of the times at which the patient responded to two verbal commands.

Drug doses, times and cardiovascular and respiratory parameters were collected using the computer-based system described by Stafford, Brooker and Hull (1984).

The dose of propofol required to induce anaesthesia was significantly higher ($P < 0.01$) in unpremedicated patients (126 ± 27 mg (mean ± SD)) than those in groups 1 and 2 (101 ± 21 mg). Induction dose did not correlate with either the age or weight of a patient The mean incremental dose rate required for maintenance of anaesthesia was 12.0 mg min^{-1} (SEM 0.52), and was not affected by the different premedication regimens.

The overall incidence of pain on injection was 3.7%, and there was no difference between the three premedication groups. No patient demonstrated involuntary muscle movement, hiccup or other excitatory effects. There was a reduction in mean arterial pressure, which correlated with the dose of propofol. By the start of surgery, values had decreased by a mean of 24 mm Hg from control. All patients developed respiratory depression with minute volumes decreasing to 40% of control values by skin preparation. However, minute volumes had recovered to 62% of control values by the end of surgery. Thirty-two per cent of patients had a period of apnoea after induction lasting for 40 s or more.

Patients recovered rapidly (median 4.7 min) and uneventfully Recovery time was related to the total dose of propofol used, but not to the premedication received. Nausea or vomiting after operation was rare in groups 1 and 3 (2.6%) In the patients premedicated with papaveretum and hyoscine the incidence was 17.5%.

We conclude that incremental propofol provides satisfactory anaesthesia with a low incidence of side effects

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ASSESSMENT OF PSYCHOMOTOR PERFORMANCE FOLLOWING I.V. DIAZEPAM OR MIDAZOLAM FOR MINOR ORAL SURGERY

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The aim of this study was to investigate the comparative effects of diazepam and midazolam on cognitive and psychomotor functioning in young adults undergoing minor oral surgery. A range of tasks was selected to determine whether the degree of impairment and rate of recovery differed across tasks and drugs. A control group was also used to ascertain whether the chosen tasks were psychometrically reliable (i.e. provided equivalent measures of performance with repeated testing).

Twenty patients received diazepam and 20 received midazolam. There were also 20 age-matched controls. All the patients completed the test battery before surgery and at 1, 3 and 5 h after sedation. The controls completed all the tests except the post-box at four equivalent times. The tests were: (i) simple reaction time; (ii) choice reaction time, (iii) letter deletion; (iv) digit symbol substitution; (v) search and memory test; (vi) the post-box test; (vii) delayed visual memory test.

The two groups of patients showed a very similar pattern of impairment and recovery. On the reaction time tests, both drugs caused significant slowing at 1 h after sedation, but recovery to baseline values was found by 3 h. The degree of impairment at 1 h was significantly greater with midazolam, since responses were over 100 ms slower than baseline values compared with a slowing of approximately 30 ms with diazepam. A similar pattern of results was found on the post-box test and on digit symbol. However, the degree of impairment at 1 h on the post-box was relatively small, possibly because of the relative insensitivity of this task. On letter deletion, performance in both groups was still impaired at 3 h after sedation, with recovery to baseline by 5 h. On some parts of the search and memory test there was evidence of continuing impairment at 3 h, but on the delayed visual memory tasks both groups were still impaired at 5 h after sedation, even though some recovery had taken place.

Overall, two broad findings emerge from the results. First, although diazepam and midazolam produce a similar pattern of impairment in psychological functioning, a consistently greater deficit is seen at 1 h after sedation with midazolam Second, the time course of recovery differs for different psychological functions. Whereas motor speed seems to show full recovery by 3 h, higher cognitive functions, particularly memory, show continuing impairments up to 5 h and possibly beyond

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MUSCLE PROTEOLYSIS AND BODY TEMPERATURE CHANGES ASSOCIATED WITH MAJOR ABDOMINAL SURGERY IN ELDERLY PATIENTS

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Body temperature decreases during major surgery as a result of a combination of factors such as an open body cavity, a cool environmental temperature and anaesthesia itself. In a previous study we showed that the excretion of urinary urea nitrogen was decreased significantly when heat loss was prevented during abdominal surgery in elderly patients (Carli, Clark and Woollen, 1982) The purpose of the present study was to investigate further this possible relationship between body temperature and nitrogen balance by measuring the urinary excretion of 3-methylhistidine after major abdominal surgery This amino acid is a constituent of actin and myosin and its excretion reflects skeletal muscle proteolysis (Ballard and Thomas, 1983).

Sixteen patients over 60 years of age who were to undergo large bowel surgery were studied. They were allocated randomly to two groups; cold (C) and warm (W). Whereas group C received routine management during and after operation, the body temperature of group W was maintained at preoperative values during surgery and for 6 h after operation. This was achieved by warming the i v fluids and inspired gases, and by covering the exposed parts of the body with warmed cotton wool padding during operation and with a metallized plastic sheet in the recovery room.

All patients were anaesthetized with a thiopentone, pancuronium and fentanyl technique and the lungs ventilated with nitrous oxide and oxygen. The mean body temperature was determined from measurements at five different sites (aural canal, upper chest, arm, thigh and calf). Venous blood samples and 24-h urine collections were taken on the day before surgery and on the 2nd and 4th days after surgery. Serum urea, creatinine, cortisol and ketone body and urinary urea, creatinine and 3-methylhistidine values were measured.

The two groups were comparable for age, body weight and height, and duration of surgery. In group C, mean body temperature decreased 2.2 °C by the end of surgery, whereas in group W the temperature increased by 0.2 °C. There were no significant differences after operation in the cortisol and ketone body values between the two groups. After operation, urea nitrogen excretion was decreased significantly in group W compared with group C, which confirms our previous findings (Carli, Clark and Woollen, 1982). Urinary 3-methylhistidine excretion, expressed as 3-methylhistidine/creatinine ratio, increased in both groups, but reached statistical significance only in group C ($P < 0.01$). We conclude that the prevention of heat loss in elderly patients undergoing major abdominal surgery results in a substantial decrease in proteolysis.

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POSTER DEMONSTRATIONS

FAILURE OF MAGNESIUM SULPHATE TO PREVENT SUXAMETHONIUM-INDUCED MUSCLE PAIN

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Magnesium sulphate has been shown to have neuromuscular blocking properties (Giesecke et al., 1968), to reduce the potassium increase following suxamethonium (Aldrete, Zahler and Aikawa, 1970) and it may abolish suxamethonium-induced fasciculations (De Vore and Asrani, 1980) On these grounds it should prove useful as a pretreatment for the prophylaxis of suxamethonium-induced muscle pain.

The incidence of muscle pain following suxamethonium was compared in two groups of unpremedicated fit, women scheduled for minor gynaecological procedures, who were ambulant shortly after operation. Informed consent was obtained from each patient. Thiopentone 5 mg kg^{-1} was given over 1 min, followed immediately by suxamethonium 1 mg kg^{-1} with maintenance using nitrous oxide–oxygen and supplementary thiopentone. In 31 patients, magnesium sulphate 1 g in 10 ml of water, was injected slowly over 2 min commencing 3 min before induction. In 35 patients pretreatment was with saline.

TABLE VIII. *Incidence of fasciculations and postoperative pain and average (± SD) duration of apnoea*

Pretreatment	Saline	Magnesium sulphate
Fasciculation (%)	89%	55%
Duration of apnoea (s)	221±53	210±57
Significant pain (%)	46%	45%

The severity of fasciculations, the duration of apnoea as indicated by diaphragmatic activity and the occurrence of pain on the 1st and 2nd days after operation was noted. Serial blood samples were taken for estimation of potassium concentration in 25 of the magnesium-treated subjects and 11 of the saline treated group.

The results (table VIII) indicate that the magnesium sulphate pretreatment did significantly reduce fasciculation ($P < 0.05$), but did not prolong the paralysis or prevent the muscle pain. Moreover, it produced unpleasant, subjective effects in conscious patients. Changes in potassium concentration in both groups were small with no significant differences between therapies.

We conclude that magnesium sulphate has no place in the prophylaxis of suxamethonium-induced muscle pain.

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INFLUENCE OF FENTANYL AND ALFENTANIL PRETREATMENT ON THE ACTION OF MIDAZOLAM

N. J. HALLIDAY, J. W. DUNDEE AND K. W. HARPER
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In younger patients and when used i.v as a sole agent for the induction of anaesthesia, midazolam is both slow in its onset of action and unreliable in producing sleep (Dundee et al., 1984). We report on a study examining the effect of opioid pretreatment of a standard induction dose of midazolam 0.3 mg kg^{-1}

The 294 patients in the study were aged between 16 and 50 yr, unpremedicated, fit and scheduled for elective surgery. Those patients, who were pretreated, were given fentanyl 50 or 100 μg or alfentanil 150 or 300 μg i.v. over 2 min, and after a further 2 min midazolam 0.3 mg kg^{-1} was injected over 20 s. The induction time was taken as that from the end of injection until the patient failed to respond to the command "open your eyes". Should a patient fail to go to sleep by 3 min, this was noted and anaesthesia completed with inhalation agents.

The incidence and rapidity of onset of sleep was significantly greater ($P < 0.001$) in the opioid pretreated group than in the control group (except $^{*}P = 0.009$ and $^{**}P = 0.003$) (table IX)

No significant difference was observed between fentanyl and alfentanil groups in frequency and rapidity of onset of sleep.

Rapidity and reliability of the induction of anaesthesia with midazolam is improved greatly by pretreatment with low doses of fentanyl or alfentanil The combination may prove useful in cases when a rapidly acting barbiturate is not suitable.

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TABLE IX. *Mean induction times ($\pm$SEM) and percent of patients asleep within 60 and 180 s following midazolam 0 3 mg kg^{-1} in patients who had no pretreatment or received either fentanyl or alfentanil*

Pretreatment	n	Age (yr) (mean±SEM)	% Asleep by 60 s	% Asleep by 180 s	Induction time (s) (mean±SEM)
Nil	110	38±3 3	20	60	113 7±1 07
Fentanyl					
50 µg	52	32±1.2	56	85	77.9±7 08
100 µg	52	34±1.1	85	92	58.2±5 71
Alfentanil					
150 µg	40	33±1 1	58	85*	76 4±5 16
300 µg	40	34±1.1	85**	90*	55.9±5 48

EFFECTS OF ISOFLURANE ON THE AUDITORY EVOKED RESPONSES IN MAN

M. NAVARATNARAJAH, C. THORNTON*, C. P H HENEGHAN AND J. G JONES
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We have shown previously that the auditory evoked response (AER) may be a useful method for assessing depth of anaesthesia (Navaratnarajah et al., 1983; Heneghan et al., 1984) Halothane and enflurane produced dose-related changes both in the brain stem (waves III and V) and in the early cortical components (waves Pa and Nb) of the AER, while etomidate and Althesin affected only the early cortical components In the present study, we have examined the effect of isoflurane on the AER to see if it produces changes similar to halothane and enflurane over a comparable concentration range

Six patients aged 28–40 yr with normal hearing gave informed consent to a procedure approved by the Harrow District Ethical Committee They were premedicated with morphine 10 mg and atropine 600 µg, anaesthetized with thiopentone 3–5 mg kg^{-1} and paralysed with pancuronium 8 mg The trachea was intubated and the lungs ventilated with 67% nitrous oxide in oxygen The end-tidal carbon dioxide concentration and oesophageal temperature were kept constant throughout the study and the arterial pressure and heart rate were monitored. Seven minutes after induction, isoflurane was introduced at a concentration of 0.75%, which was maintained for a period of 10 min. The inspired isoflurane concentration was then increased in four equal increments to a final concentration of 3.75%, each concentration being maintained for a period of 10 min. Inspired and end-tidal isoflurane concentrations were measured continuously using the Engstrom EMMA The AER was recorded before and after induction of anaesthesia and during the latter half of each 10-min period at each concentration

Isoflurane produced significant dose-related changes in the early cortical components of the AER these were an increase in the latency of waves Pa and Nb ($P < 0.001$) and a decrease in their amplitude ($P < 0.001$). There were also effects on the brain stem components These were a significant increase in latency ($P < 0\ 01$) and reduction in amplitude ($P = 0.05$) of wave V, and an increase in wave III latency which approached significance ($P = 0\ 06$)

In conclusion, the effects of isoflurane on the AER were similar to those of halothane and enflurane over a comparable concentration range· thus all three inhalation agents affect both brainstem and early cortical components, unlike the i.v agents which affect only the early cortical waves.

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COGNITIVE EFFECTS OF GENERAL ANAESTHESIA IN YOUNG AND ELDERLY PATIENTS

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The psychological consequences attributed to anaesthesia and anaesthetic agents have been examined by a number of authors, yet continue to be a source of controversy For example, although Drummond (1975) lists over 100 references bearing upon the problems of changes in mental functioning after anaesthesia, there is no general consensus of opinion concerning the putative relationship between cognitive deficits and anaesthesia

The present study was designed to determine whether a typical general anaesthetic procedure produces postoperative cognitive deficits in young and elderly patients. Eighty-five patients undergoing elective surgery were assessed on a battery of standardized cognitive tests, measuring orientation in time and place, concentration and short-term memory, 1 day before surgery and 2 days after the operation Particular attention was paid to the possibility that the anaesthetic process contributed to any deterioration that occurred

Analysis of results indicated that the anaesthetic procedure produced significant short-term memory deficits after operation in both young and elderly patients, and significant deficits in concentration and orientation in time and place in elderly patients Possible causative mechanisms underlying these deficits can be identified, and research is currently underway to test out these mechanisms.

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CORRESPONDENCE

SUXAMETHONIUM SPASM

Sir,—We read with interest the retrospective study of Ellis and Halsall (1984) concerning the significance of "suxamethonium spasm" in patients screened for malignant hyperthermia (MH), and would like to take issue with their interpretation of, and the conclusions drawn from, their data.

The subject at issue is "suxamethonium spasm", so patients to whom suxamethonium was not administered or for whom information was incomplete or unavailable, should not be included. Therefore, rather than analysing 277 patients, the relevant population to be analysed is 156, of whom 99 fall into their MHS group and 57 into the MHI group. The relative incidence of "spasm" following suxamethonium is then 65% in the MHS group and 63% in the MHI group—indicating that there is no difference in the incidence of "suxamethonium spasm" between the two groups. We are, unfortunately, not told how many of the MHI group with "suxamethonium spasm" had definite signs of MH, neither is there any information as to whether alternative diagnoses were looked for or existed in the MHS group, and we are not informed as to the criteria used to qualify for "rigorous" MH screening. Provision of such information would allow for a more critical comparison of the two groups. Furthermore, the significance of *in vitro* MH muscle testing in abnormalities and diseases other than MH has not been determined. As noted in their paper, "spasm" of muscle in association with suxamethonium use is not uncommon, but differentiation between normal, exaggerated and abnormal responses can prove difficult.

Suxamethonium, an endplate agonist, causes contraction of muscle fibres at the initial agonist–receptor formation; subsequently, relaxation occurs in the continued presence of suxamethonium. The effects of suxamethonium on the individual fibres, the whole muscle, and the agonist–antagonist combination of functional muscle groups depend in part on the distribution of blood flow (Bowman and Rand, 1980). These responses may appear as fasciculations, increased tone or visible movements; these phenomena are variable in time and can be interpreted as "spasm". The failure to relax after the initial contraction is known as a contracture, as originally described in multiply innervated amphibian tonic muscles; a contracture is apparent as an increase in tone. Most mammalian muscles do not usually respond in this fashion. Normal, multiply innervated, avian skeletal muscles, however, seem to freeze in the position commensurate with the relative strength of the agonist and antagonist muscle groups, they can appear board, stiff or rigid (Bowman and Rand, 1980). A similar type of rigidity can be observed in the porcine MH syndrome and has been reported in cases of human MH. Rigidity in the last two syndromes is usually accompanied or followed by excessive rates of metabolism, rapid temperature increases and, subsequently, by cardiorespiratory collapse (Gronert, 1980). This rigidity, interpreted as "spasm", may herald the onset of MH. Incomplete or aborted forms of MH have been proposed to explain symptoms or signs, such as "masseter spasm", in the absence of "definite signs" of MH (Donlon, 1978). Unfortunately, an adequate definition of suxamethonium spasm is not provided by Ellis and Halsall (1984).

Other altered responses to suxamethonium include the increase in tone of human extraocular muscles (Bowman and Rand, 1980), of denervated muscles (Bowman and Rand, 1980) and localized or generalized rigidity in patients with myotonic dystrophy or congenital myotonia (Paterson, 1962, Thiel, 1967; Cody, 1968). An increase in tone may occur in the muscles of mastication of "normal healthy" humans during the induction of general anaesthesia with halothane and suxamethonium, leading to an initial difficulty in opening the mouth before intubation. This latter phenomenon, interpreted as "masseter spasm", has been observed by us, in particular in children, and others during "routine" general anaesthetics without the subsequent development of MH and without a history of any prior disease. In such cases, while continuing general anaesthesia with halothane, we have waited until the jaws relaxed, intubated the trachea and proceeded with anaesthesia using appropriate monitoring, for periods in excess of 1 h. Perhaps the muscles of mastication of (some) children show a response to suxamethonium (and halothane) which is akin to the response of human extraocular muscles or of other multiply innervated muscles, it may be that this contractile property, elicited by suxamethonium (and halothane), is lost or modified during maturation.

It may be that, for example, "spasm" of the muscles of mastication represents a variant response to suxamethonium plus halothane, but in order to determine the true association between abnormal responses to suxamethonium (such as "masseter spasm") and different (disease) entities (such as MH), one needs to ascertain the incidence of the abnormal response (such as "spasm") in prospective, controlled, randomized trials in appropriate populations, preferably using objective measurements (such as of tone and force developed), and not by retrospectively analysing a pre-selected cohort already under investigation for MH. Only after the determination of the distribution of the occurrence of "spasm" would one be able to express probability of occurrence of a disease with a predictive value once "spasm" is observed in a patient who received suxamethonium (MacMahon and Pugh, 1970).

We feel strongly that this paper does not substantiate the claim that "suxamethonium spasm" probably indicates the presence of MH and we are concerned that every patient with an exaggerated or variant respone to suxamethonium will be labelled "MH susceptible".

However, until the significance of "suxamethonium spasm" has been established, it might be prudent for the anaesthetist to institute monitoring for MH in order to decide on treatment and, furthermore, to consider referral of that patient to an appropriate medical facility for evaluation.

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N Wilton
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SIR,—We welcome an opportunity to respond to the important issues raised in the letter of Drs VanDerSpek and Wilton.

"Suxamethonium spasm" is a clinical observation which therefore defies accurate definition. The patients we analysed were referred to this laboratory after an "event" which raised the suspicion of malignant hyperpyrexia (MH) The inclusion of all referrals, and not only those with suxamethonium spasm, was to enable the reader to observe the incidence of the condition.

Spasm following suxamethonium, which can be "defined" as a sustained increase in skeletal muscle tone sufficient to hinder intubation or passive movements of the limbs, is uncommon. So too is MH. Therefore if 50% of patients with the one are found to have the other, this is an important association which cannot be glibly dismissed as by your correspondents, who state "indicating that there is no difference in the incidence between the two groups" They clearly have not appreciated that the two groups under discussion exist ONLY after *in vitro* MH screening. If the diagnostic tests were not performed we would see only one group containing 50% MH susceptibles—but which 50% is which?

The message we wished to convey seems to have reached the target. We are delighted that Drs VanDerSpek and Wilton concluded their letter by paraphrasing the most important point of our paper (which was even included in the summary of the latter) namely, "however, it might be prudent to monitor for MH and to consider referral to an appropriate medical facility".

F. RICHARD ELLIS
P JANE HALSALL
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SPINAL MORPHINE IN ENURESIS

SIR,—Many authors point out that urinary retention is a side effect of the subarachnoid injection of morphine, and urodynamic investigations have demonstrated that detrusor muscle activity is decreased soon after the extradural administration of morphine, and this is associated with an increase in bladder capacity (Rawal et al , 1983) In contrast, children with enuresis were found to have a more active detrusor and a smaller bladder capacity when compared with normal subjects (Lindeholm, 1966) If these two findings are valid, could the subarachnoid injection of morphine benefit children with enuresis?

A random group of 75 young patients (54 boys), ranging in age from 5 to 19 (12 4) yr were treated between December 1982 and April 1984. The enuresis was labelled as primary in 48 patients and secondary in the other 27. Twenty children wet the bed only intermittently.

As both the parasympathetic and sympathetic nerves are involved in micturition, the morphine was injected, on one occasion, as described by Eriksson (1970), at two spaces. T11–12 (extradural) and L2–3 (subarachnoid). Morphine hydrochloride was administered according to the body weight: (subarachnoid) 0.25–1.5 mg in 0.25–1.5 ml of normal saline; (extradural) 1–5 mg in 2–7 ml of normal saline Following treatment, the patients were placed in an intensive care unit for about 48 h They were allowed fluids

Severe itching was noticed in the great majority of the patients, and nausea and vomiting in 65. Sedation was marked in 68 patients. Six children developed respiratory depression, 5 h after morphine injection Of these, two had the lungs mechanically ventilated and the rest required large doses of pimeclone (a central nervous system stimulant). Naloxone was deliberately omitted.

Interesting results were noted regarding the act of micturition
Urinary retention for about 12–36 h in 24 patients.
Improvement in the sensation to pass urine, and a decrease in the micturitions per day, in all reliable children.
Twelve patients showed no improvement.
Twenty patients completely stopped bedwetting.
Fifty-three continued to wet the bed, but more rarely. Forty of these had periods of 1 week to 2 months when they did not wet the bed

The reversal of urinary retention after subarachnoid morphine and recent experimental (cats) investigations (Jubelin et al., 1984) suggest a role for endogenous opiates in micturition. Our results are clinical evidence of such a role. All the side effects noted in this study are in accordance with the known rostral migration of morphine (Bromage et al , 1982). The high incidence of respiratory depression is surely the result of the large doses of morphine injected. The two levels were used to penetrate as many nervous structures as possible. That is why large quantities of pimeclone were necessary to antagonize the respiratory depression

Many patients showed no improvement, as urinary retention was not present in all cases. Urinary retention as a side effect of subarachnoid morphine rarely exceeds 24 h. However, the partial and the good results obtained in this study were long in duration,—in some patients for 15 months

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AIR BREAK RECEIVER UNITS

SIR,—The three articles on this subject (*Br J. Anaesth* (1983), 55: 661, 671, 681) provide details of the performance of some cumbersome devices to scavenge anaesthetic gases. Unfortunately, the inconvenience and expense of these devices militate strongly against their acceptance, and are largely responsible for the deplorable British record for the use of scavenging systems.

Since none of the three articles makes any reference to the Northwick Park Hospital system (*Br Med. J* (1976), 2, 1219) we feel that your readers should be reminded of the existence of this simple and effective system, which has been in continuous use

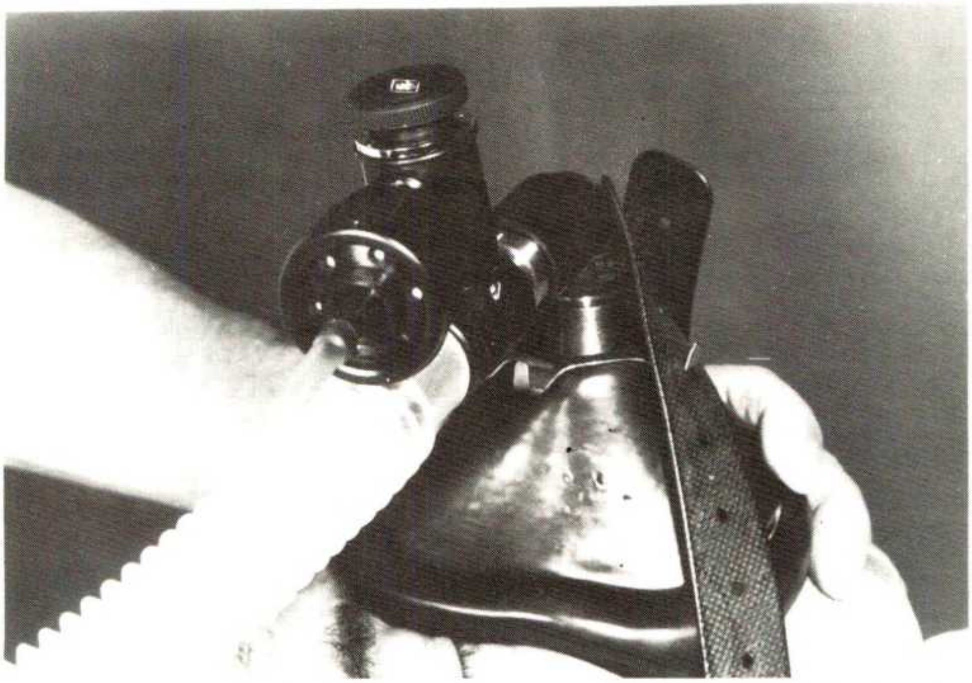

FIG. 1. Northwick Park Hospital air break, in use. Note the ring of six recessed holes which limited the negative pressure to 1 cm H_2O at 40 litre min^{-1} suction. The relatively large size of the device compared with the suction pipe is necessary because of the British Standards specification for a 30-mm fitting.

here for 9 years. A plastic miniature air break (fig. 1) with a proximal reservoir bag, when required, is attached to any anaesthetic circuit gas release point and extraction is through the theatre suction line or any other system giving the required 40-litre min^{-1} air flow. The air break prevents any possibility of a strong negative pressure being communicated to the patient and limits the positive pressure, if suction should be inadvertently interrupted, to a few centimetres of water.

This system has been shown to decrease contamination below the very rigorous limit set by the American NIOSH (*Anaesthesia* (1980), **35,** 554). It is extremely simple to use and, since no engineering works are required, the cost for a major hospital is only of the order of £500, if the central theatre suction is used. Dire warnings about the effect on the pumps of the central vacuum system have proved to be totally unfounded, and our, and many other hospitals have ample spare capacity (*Br. Med. J.* (1978), **1,** 918). We believe that the trend for more cumbersome and expensive systems, and for new regulations which are even less likely to be applied in practice is totally unrealistic, misdirected and, in these times of financial stringency, inappropriate. We would like to suggest that potential users should consider this well-tried, inexpensive and highly convenient system.

H. T. DAVENPORT
J. F. NUNN
B. M. WRIGHT
London

Sir,—We appreciate the comments of our colleagues at the Northwick Park Hospital on our and other Air Break Receiver Units, but cannot accept their view that these are in general overdesigned.

It is important that, in protecting the staff from the somewhat unquantified hazards of pollution by waste anaesthetic gases, we do not cause a fresh hazard for the patient. To this end, stringent standards have been laid down by the Department of Health and Social Security (DHSS) for safety and performance of air break units (Department of Health and Social Security, 1980). We believe these standards are reasonable and must be respected by equipment designers and that, in particular, attention must be paid to possible malfunctions introduced by the rigours of the working environment. Our experience has shown that many simple units do not perform safely when tested in this way. Paper or plastic film can be drawn into the relief ports of air break units not provided with a cover having vents of large area. We feel that a test simulating these conditions should be applied to all systems, since a fault of this nature applies a negative pressure of many kilopascals to the patient.

The Northwick Park Unit, a sample of which was kindly supplied by Dr Martin Wright, when tested, achieved the performance claimed by its designers at the recommended scavenge rate of 40 litre min^{-1}. The scavenge flow in the unit is, however, not regulated and depends on the mode of connection to the vacuum line and can reach 60 litre min^{-1} via a Medishield Vacuum Controller or 75 litre min^{-1} when connected directly to a suction point by 4.5 m of 8-mm hose. At these high flow rates, negative pressures which could be applied to the patient reached –350 Pa (seven times the DHSS limit of –50 Pa.). When plastic film was brought in contact with the relief holes of the unit at flow rates greater than 40 litre min^{-1}, the film was held in place by the suction and drawn down onto the relief holes. The result of negative pressure applied to the APL valve depended on chance bedding down of the sheet and varied from –4 kPa to –20 kPa in a series of tests. Although the chance of such a fault occurring is extremely small, the consequences are so serious as to make the possibility unacceptable.

We have no objection to the use of the hospital vacuum line as a disposal system for individual units, since the Barnsley air break system is quite safe to use in such a manner. We agree that the use of the hospital vacuum as a disposal system will have no adverse effects on the pumps (Enderby, Booth and Churchill-Davidson, 1978), but there are other engineering considerations. A vacuum point is required for the continuous use of the surgeon and another for the emergency use of the anaesthetist. Few theatres, even the most modern, can provide a third point for use permanently with scavenging systems; thus some engineering work is required on this account, even if no dedicated disposal line is installed.

Hospital vacuum systems are rated to deal with accurately predicted flow rates related to the normal use of the points. If the additional large flow rate demanded by a scavenging system is to be provided by the hospital vacuum system, the plant must be uprated to take account of the higher flow rates. Whether the extra flow capacity is provided by uprating the vacuum system or by installing a dedicated scavenging system, expense is incurred. It seems reasonable, therefore, to provide a dedicated disposal system for waste anaesthetic gases, with the extra security that this offers in return for the small extra costs incurred.

In conclusion, the major concern in the design of anti-pollution equipment must be the safety of the patient. Although the unit may have proved satisfactory under the ideal conditions of the Northwick Park Hospital, we would not be happy to use it in a busy General Hospital unless the negative pressure relief valve was placed between the air break unit and the patient circuit. As a proximal reservoir bag is also required to accept the discharge of mechanical ventilators, these might be combined as in the Penlon safety block. When used in this way, the Northwick Park device becomes a machine-mounted system and surrenders its claims to cheapness and simplicity without reaching the very high levels of safety and silence embodied in the Barnsley Receiver.

Sir Basil Houldsworth
J. O'Sullivan
M. Smith
N. Musgrave
Barnsley

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OBSERVATIONS ON "JUNCTIONAL RHYTHMS" DURING ANAESTHESIA

Sir,—The correspondence from Sethna, Deboer and Millar (1984) would seem to imply that these observations on the three forms of junctional rhythm have not been previously described and classified in relation to anaesthesia. Most of the comments that they have made on isorhythmic dissociation are covered in considerable detail in two chapters in Prys-Roberts (1980). Both Smith (1980) and I discussed at length the nature and mechanisms responsible for the development of junctional rhythm, and included a critical review of the existing literature at that time. The haemodynamic consequences of the transient changes from sinus rhythm to isorhythmic dissociation are well depicted, both as regards "cannon" waves and the secondary effect on myocardial perfusion. I would agree with Dr Sethna and his colleagues that true wandering pacemaker or AV nodal rhythm with inverted P waves are very uncommon during anaesthesia, while isorhythmic dissociation is an everyday event.

C. Prys-Roberts
Bristol

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TACTILE OROTRACHEAL INTUBATION

Sir,—We read with the greatest interest Dr Tunstall's report (Tunstall and Geddes, 1984). We would like to draw attention to another method that could be a valuable alternative in such a case: the tactile orotracheal intubation. This very old and often forgotten technique (MacEwen, 1880) has been recently refined (Stewart, 1984) and has the major advantage of not requiring any movement of the head and neck and, especially, not needing any sophisticated apparatus. This would be particularly important when difficulties occur on "the firing line".

Y. Gregoire
A. Gouder
P. Ravez
Boussu, Belgium

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Tunstall, M. E., and Geddes, C. (1984). "Failed intubation" in obstetric anaesthesia. An indication for use of the "oesophageal gastric tube airway". *Br. J. Anaesth.*, **56**, 659.

Sir,—With regard to bringing tactile orotracheal intubation to the attention of your readers, it may stimulate people to try it and report back on it. The writers of the letter do not indicate whether they themselves have tried it on a 116-kg mother with large breasts, receiving cricoid pressure, with a possible full stomach, fetal distress etc!

M. E. Tunstall
Aberdeen

HYPOXIC VENTILATORY DRIVE IN THE DOG UNDER ALTHESIN ANAESTHESIA

Sir,—I was concerned to read the paper by Dr Gaudy and his colleagues (1984) entitled "Hypoxic ventilatory drive in the dog under Althesin anaesthesia". The steroid combination of alphaxalone and alphadolone is solubilized in saline by Cremophor EL. The preparation has the trade names "Althesin" (Glaxo) and, for veterinary use, "Saffan" (Glaxovet). In veterinary anaesthesia, the preparation is licensed for use only in cats and monkeys. The data sheet states specifically "Saffan is contraindicated in dogs because the solubilising agent causes the release of histamine or histamine-like substances in this species."

There is, however, one reference in the literature to the use of the drug in canine anaesthesia (Corbett, 1977). This author recommends the routine premedication with the anti-histamine drug chlorpheniramine plus acepromazine. It was noted that some dogs still showed signs of adverse reaction to the solubilizing agent, with urticaria and hyperventilation.

It is surprising that the authors did not report any of these signs in their series of eight Beagles, particularly in view of the fact that they were not premedicated. Whilst the authors reported that a catheter was inserted to the femoral artery for the recording of arterial pressure, no record of these measurements appears in the results section.

In view of the problems which are likely to be caused by the anaesthetic agent, I would suggest that it is inadvisable to use this type of animal preparation.

R. S. JONES
Liverpool

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Sir,—It is extremely difficult to understand why Drs Gaudy, Bergeret, Boitier and Ferracci (1984) chose dogs as the experimental animals for their study of the hypoxic ventilatory drive under Althesin anaesthesia.

It is well known that the Cremophor EL constituent of Althesin causes histamine release in Canidae and, indeed, its magnitude is well documented in the preceding paper by Glen and Hunter (1984). The results of the study are likely to have been influenced by this. Did the authors have some particular reason for their choice?

L. W. HALL
Cambridge

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Glen, J. B., and Hunter, S. C. (1984). Pharmacology of an emulsion formulation of ICI 36 868. *Br. J. Anaesth.*, **56**, 617.

Sir,—Two questions have been asked by Drs Jones and Hall: why was Althesin used in the study of hypoxaemic stimulus effects and why did we select the dog as the experimental animal,—since it is well known that Althesin induces, in the dog, the release of histamine, and raises the possibility of interference with the results of our observations.

We decided to study the hypoxaemic stimulus under Althesin anaesthesia for several reasons: (1) it has not yet been investigated with this anaesthetic agent, neither in animals nor in man; (2) Althesin offers the possibility of inducing long-term anaesthesia which is easily reversible, and of obtaining a stable ventilatory state lasting at least 60 min when it is administered i.v. (Sear and Prys-Roberts, 1981); (3) with this experimental model, the modifications of ventilation, such as those occurring after drug administration (e.g. oxygen), do not modify the depth of anaesthesia; this is not necessarily the case with inhalation anaesthetics, since the plasma concentration depends to some extent on alveolar ventilation; (4) anaesthesia can be induced and maintained with Althesin alone, thus preventing possible effects caused by premedicants, and interactions between Althesin and such drugs.

The histamine releasing effect of Althesin in the dog is well known: it causes a more or less generalized erythema of the skin, oedema of muzzle and paws, and a decrease in systemic arterial pressure (Gaudy et al., 1982). Cremophor EL, solvent of the steroid anaesthetic agent, may also release histamine (Lorenz et al., 1977). When alphadolone and alphaxalone are dissolved in dimethylsulphoxide, the above-mentioned accidents do not occur (unpublished personal observations). It should be noted that, with the technique we have used (slow injection of a diluted solution of Althesin), such accidents have been noted, but in less marked form, and they were of short duration. In particular, systolic arterial pressure does not decrease to less than 10.60 kPa (80 mm Hg). The return to normal values is obtained spontaneously within 60–90 min. The return to normal values may be obtained more rapidly by infusing 200–250 ml of plasma expander.

Would the release of histamine modify the observed results? To begin with, it might be useful to determine whether the plasma concentration of histamine is abnormal 2 h after inducing anaesthesia (average time required for obtaining a stable state). This should be possible, and yet it seems most unlikely. In point of fact, after a rapid i.v. injection (6 min) of a significant quantity of cremophor EL in dogs (300–400 mg kg^{-1}) (unpublished personal observations), the plasma concentrations of histamine at 2, 5, 10, 30, 90 and 150 min after injection were 201, 7703, 77 141, 15 956, 2231 and 960 ng ml^{-1}. It is likely that, with the technique used in our study, the plasma concentrations of histamine were much lower. This is worth checking. Even if, at the time of the present study, the histamine concentrations were abnormally high, it is most unlikely that they were capable of modifying the observed results, because the ventilatory modifications caused by Althesin in the dog (Gaudy et al., 1982) are similar to those caused by thiopentone (Gaudy et al., 1983), and histamine acts mainly on the pulmonary receptors (J-receptors, irritant receptors) (Paintal, 1981), whereas it does not seem to affect ventilatory control. Indeed, in a recent study (Arrang et al., 1983), the existence of histamine receptors at the level of the central nervous system has been reported; however, the role of these receptors in ventilatory control has not yet been determined.

J. H. GAUDY
Paris

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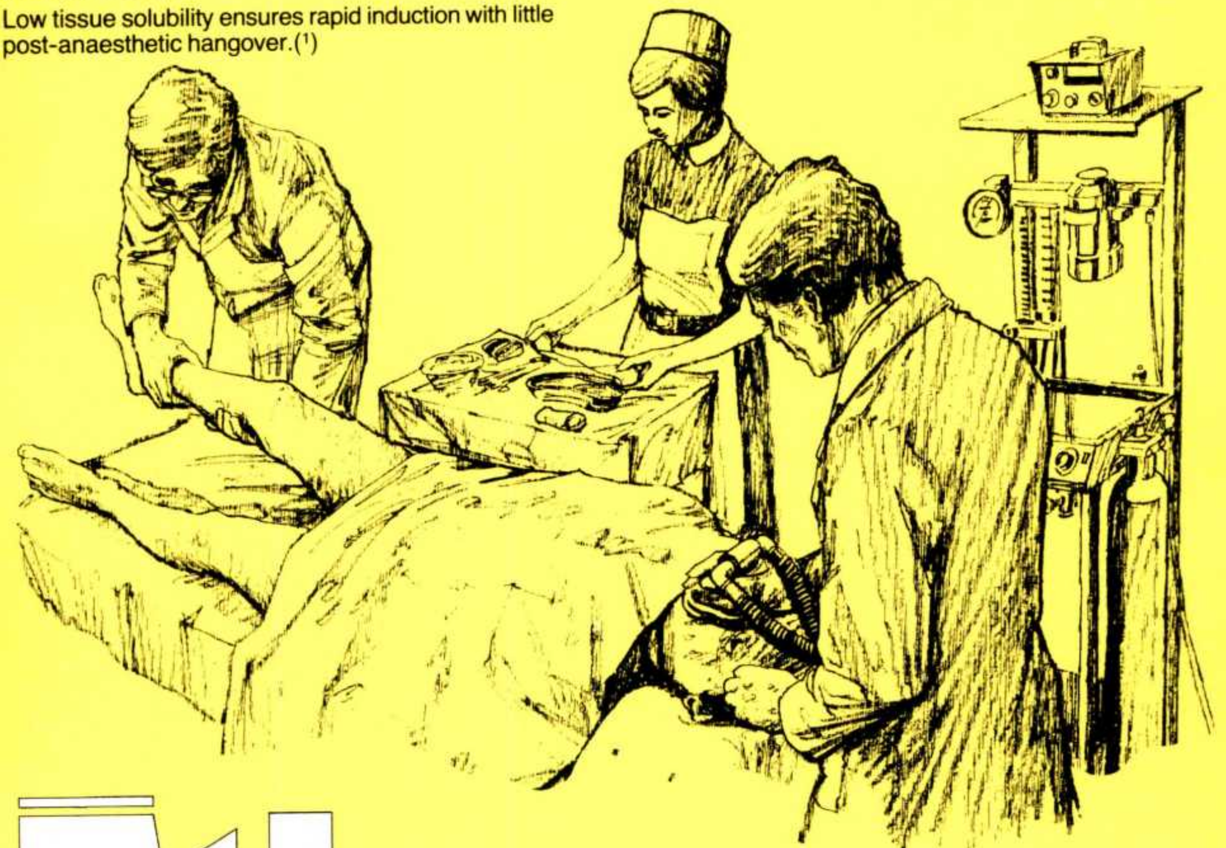

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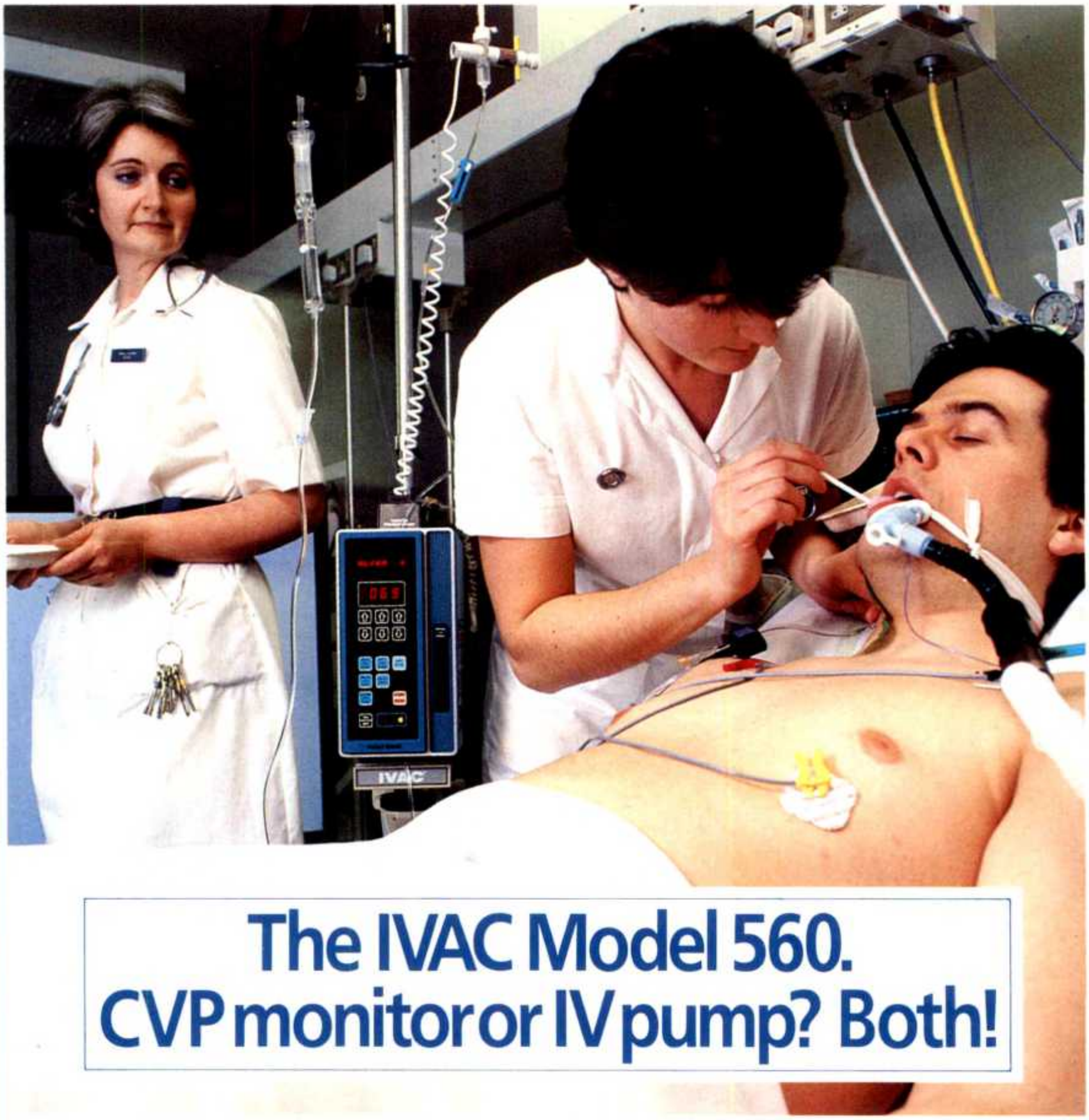

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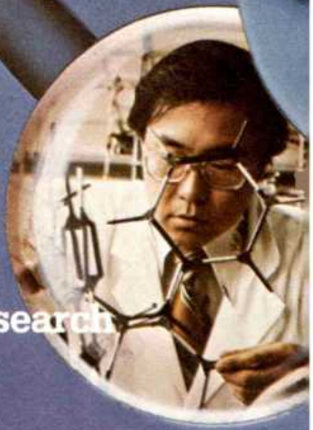

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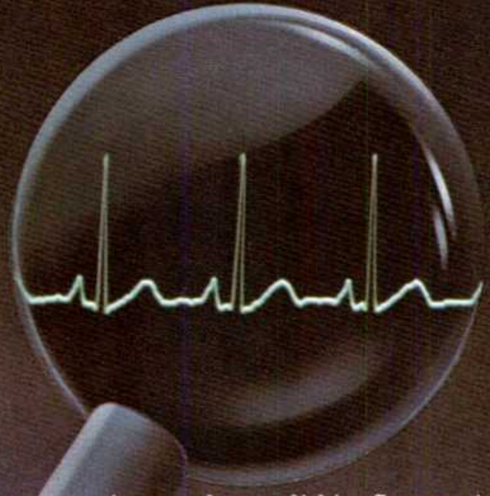

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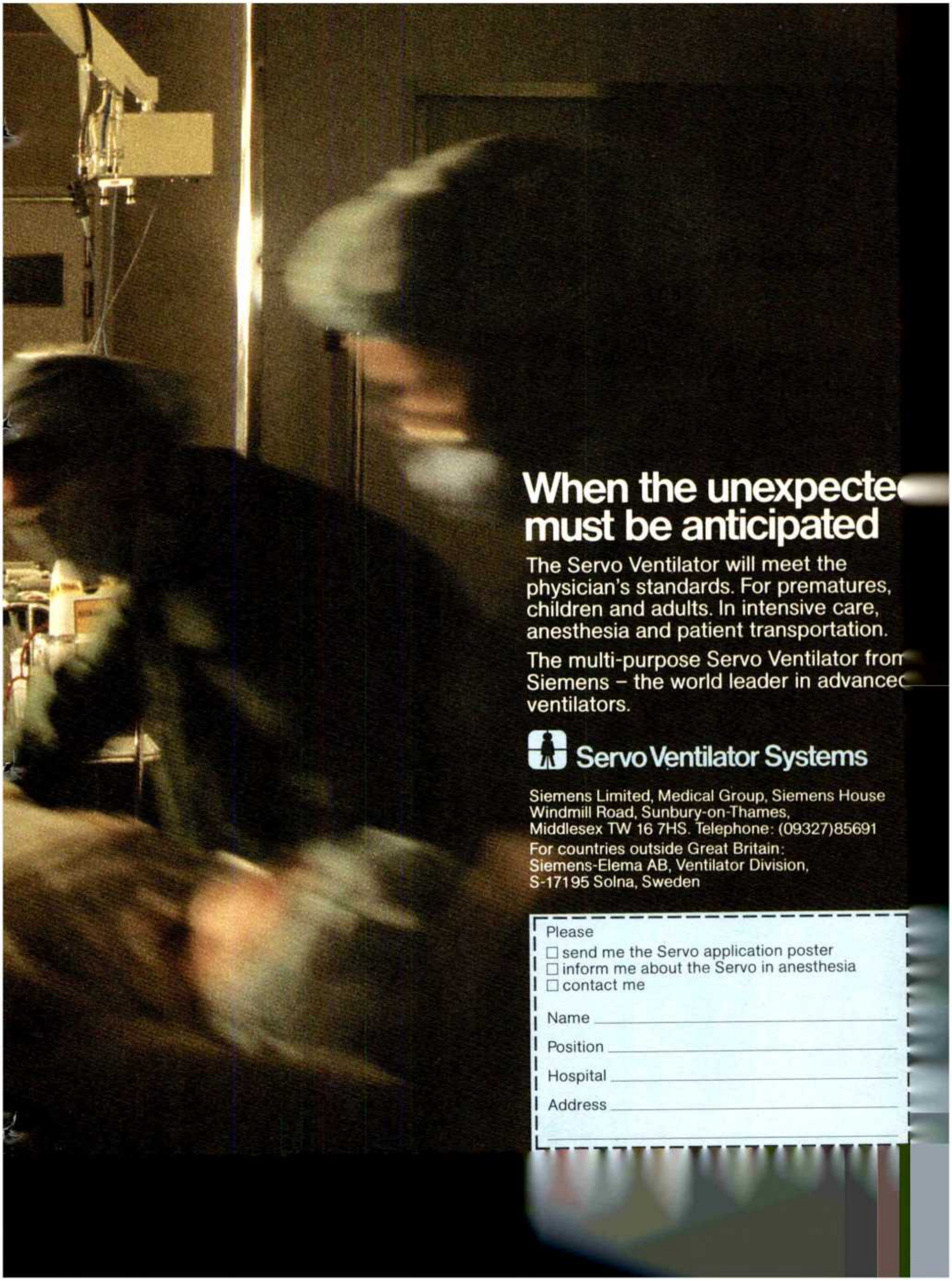

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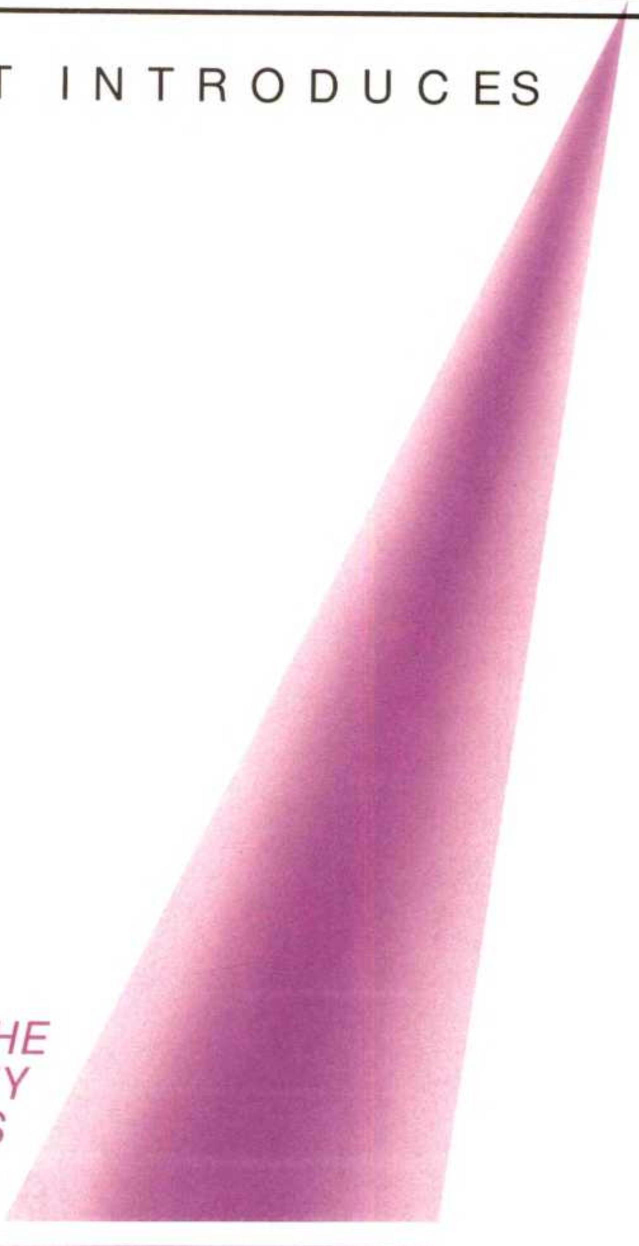

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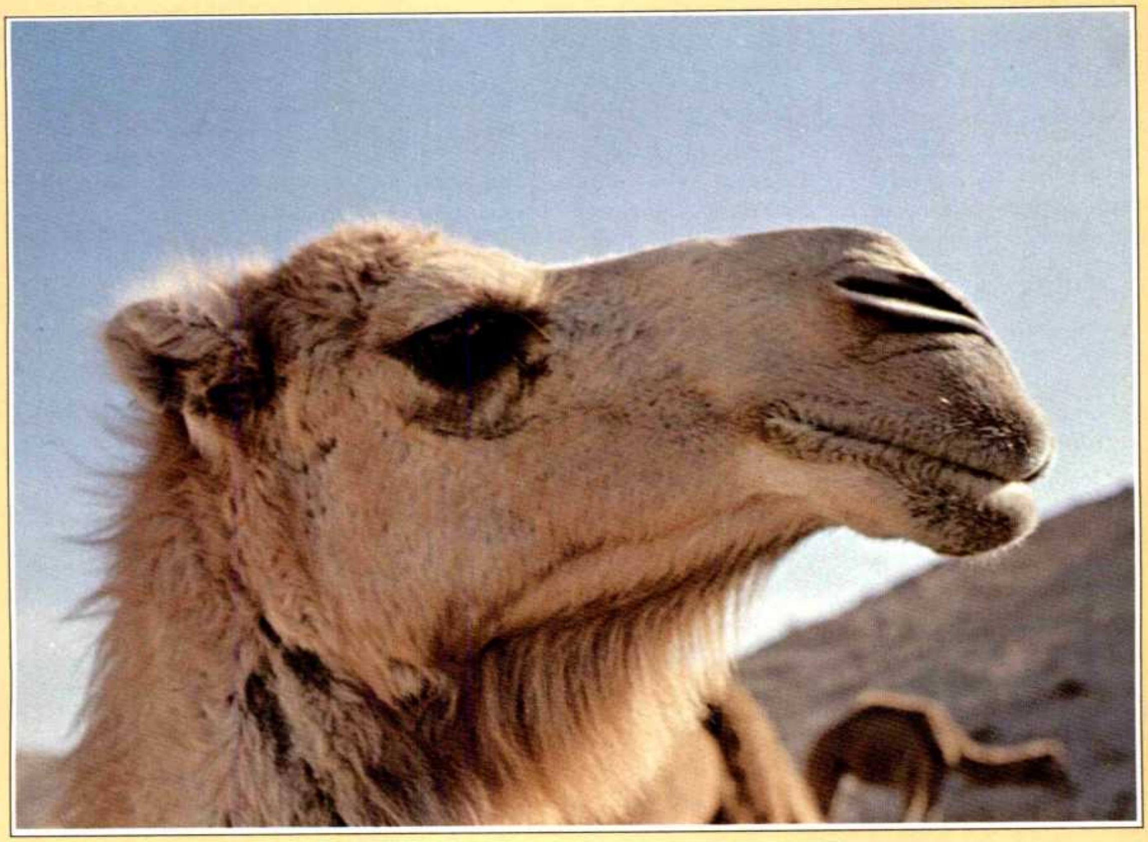

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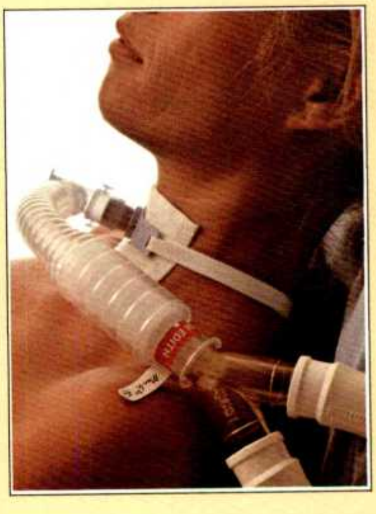

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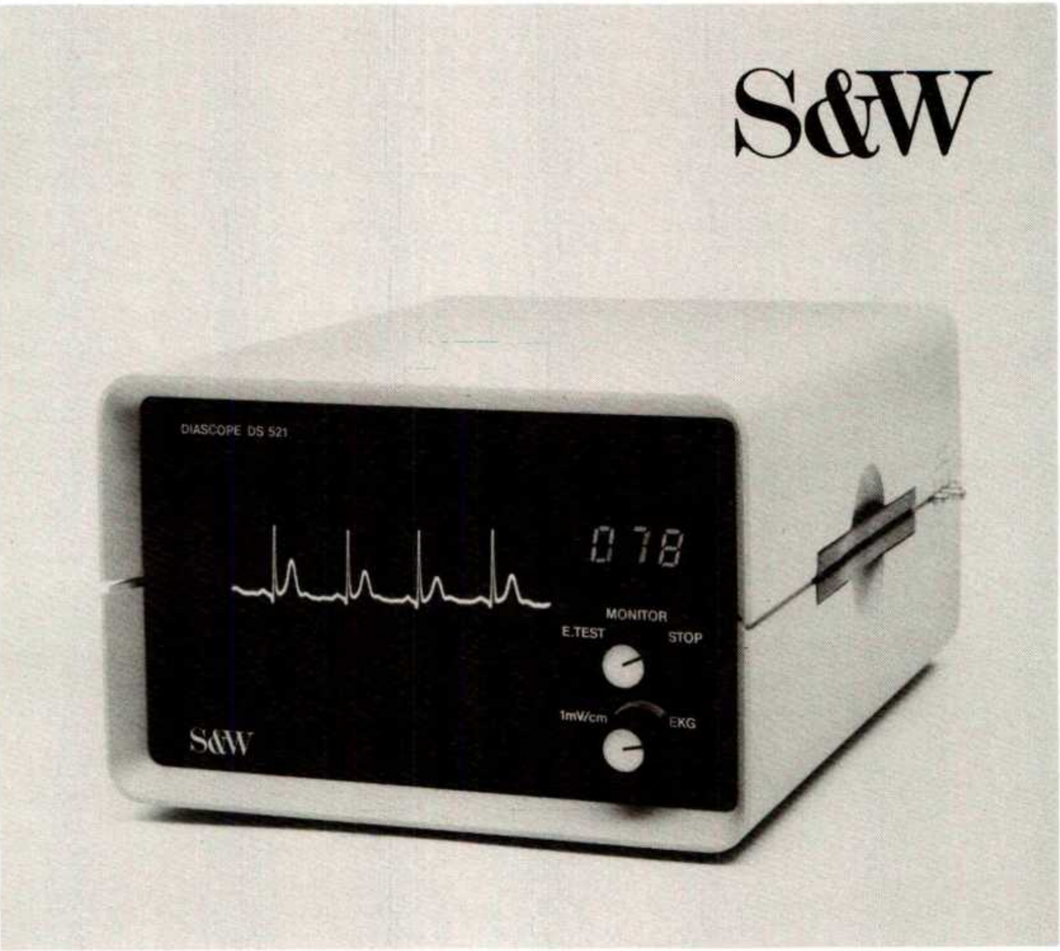

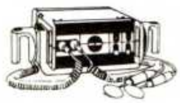
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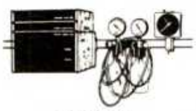
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BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

"He looks a little blue down this end"

MONITORING OXYGENATION DURING ANAESTHESIA

Although hypoxia occurs during anaesthesia, it is usually transient and of little or no clinical consequence. Most often it follows apnoea or airway obstruction during induction of anaesthesia where it may be readily recognized and treated, although it may occur during stable general anaesthesia in apparently normal subjects (Nunn, 1977). In addition, hypoxia frequently accompanies certain procedures such as dental anaesthesia, bronchoscopy, direct laryngoscopy and "one-lung" anaesthesia, but here its presence may be anticipated and countered.

Less frequent and therefore less expected is the hypoxia of an unrecognized pneumothorax, oesophageal intubation or disconnection of the anaesthetic circuit. Failure of the oxygen supply and the delivery of a hypoxic gas mixture is a continuing source of anxiety, not least because many of these mishaps occur in otherwise healthy subjects.

Clinical detection of hypoxia by the observation of cyanosis is dependent, not just on the Pa_{O_2}, but also on skin blood flow and the haemoglobin concentration. Plethoric individuals frequently display facial cyanosis in the supine or head-down positions despite a normal Pa_{O_2}. Cyanosis can be detected by experienced observers in 95% of patients with an arterial oxygen saturation of (Sa_{O_2}) of 89% (Kelman and Nunn, 1966). Most anaesthetists would regard the corresponding Pa_{O_2} of 7.7 kPa as unacceptable. The ambient lighting and the site examined also influence the ability to detect cyanosis. A reliance on clinical observation to detect hypoxaemia would seem to be at best unwise.

Many authors have called for the widespread use of oxygen concentration monitors (Cundy and Baldock, 1982; Dorsch and Dorsch, 1983) and disconnection alarms (Cooper, Newbower and Kitz, 1984), but they are not used widely in this country. Apart from considerations of cost, it may be conjectured that the low usage of these monitors is attributable to their inability to warn of all possible causes of hypoxia. A more fundamental objection is that the relative rarity of incidents likely to produce an alarm breeds a false sense of security and an inoperative or incorrectly adjusted monitor will pass unnoticed. Instruments which detect hypoxaemia directly in the patient would seem preferable. If, in addition to their alarm function, physiological changes could be deduced, it would be more likely that their proper functioning would be observed and verified more often. Two techniques fulfil these requirements: transcutaneous oxygen measurements and oximetry.

Clark-type transcutaneous oxygen (tcO_2) electrodes are widely used in neonatal intensive care and anaesthesia. The thin skin of neonates makes possible a good correlation between arterial Pa_{O_2} and Ptc_{O_2}, which is not the case in adults, particularly in conditions of poor skin perfusion. However, as Shoemaker and Vidyasagar (1981) have pointed out, it is wrong to regard the Ptc_{O_2} as a non-invasive Pa_{O_2}, and it is best considered as a measurement of cutaneous oxygen delivery. Thus, while a useful tool in anaesthesia for major surgery and the critically ill (Tremper and Shoemaker, 1981), it cannot be regarded as a simple monitor of arterial oxygenation. The calibration and stabilization time, generally around 20 min, also make it unsuitable for routine use.

Oximeters measure the percentage oxyhaemoglobin saturation by passing light of differing wavelengths through tissue. The original instruments were difficult to use, being bulky, difficult to calibrate and sensitive to changes in ambient light. They were also susceptible to inaccuracy when skin perfusion was poor despite heating the tissue to ensure arterialization. The latest generation of pulse oximeters utilize a different principle whereby the modulation of transmitted light caused by arterial pulsation is detected. The absorption of light by non-pulsatile tissue and venous blood is thus distinguished from the light absorbed by arterial blood. The tissue only has to be heated sufficiently to ensure an adequate arterial pulsation. The probes are much smaller than previous oximeters and are approximately the same size as conventional finger or ear plethysmographs. Stabilization times are generally less than 3 min and often less than 1 min.

Increased concentrations of carboxyhaemoglobin and bilirubin will interfere with the measurement of Sa_{O_2}. Marked venous pulsation from tricuspid incompetence will also decrease falsely the indicated Sa_{O_2} when pulse oximeters are used.

The shape of the oxyhaemoglobin dissociation curve is the major disadvantage to the use of oximetry. Large changes in Pa_{O_2} may occur if Pa_{O_2} is high with only minor changes in Sa_{O_2}. However, if 10 kPa is regarded as the lowest acceptable Pa_{O_2} then the corresponding Sa_{O_2} of 95% can be readily distinguished from the normal Sa_{O_2} of 98–100%. Thus, changes in oxygenation with position and anaesthetic technique, for example, the administration of halothane, can be detected, giving an insight into otherwise undetectable physiological changes.

Pulse oximeters would appear to be the most convenient method currently available for monitoring oxygenation during anaesthesia (Byrick, 1984). While their use in procedures and subjects where hypoxia might be expected can clearly be justified, the cost-benefit in routine anaesthesia is less obvious. The increasing frequency and cost of litigation in the United States has led at least one malpractice insurance group to advise its members that oximetry is becoming a "care-standard" for anaesthetic practice and that, in the near future, failure to use such monitoring could be construed as negligence (Rubsamen, 1984). This stance may seem extreme but, given the difficulty in detecting hypoxia clinically, the place of monitors of oxygenation in anaesthetic practice deserves wider consideration.

C. D. Hanning

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Br. J. Anaesth. (1985), 57, 361–368

COMPARISON OF ETOMIDATE AND ALTHESIN IN THE REDUCTION OF INCREASED INTRACRANIAL PRESSURE AFTER HEAD INJURY

N. M. DEARDEN AND D. G. McDOWALL

The measurement of intracranial pressure (ICP) following severe head injury has led to the use of aggressive intensive care management regimens in attempts to decrease the mortality associated with severe post-traumatic intracranial hypertension. Reports during the early 1970s suggested that use of barbiturates to control ICP might improve mortality without increasing morbidity in patients with post-traumatic diffuse brain swelling (Shapiro et al., 1974). However, the tendency for barbiturates to cause hypotension (Schulte am Esch, Pfeifer and Thiemig, 1978) and to prolong recovery following cessation of the drug has led to the investigation and use of shorter-acting anaesthetic agents to control the increases in ICP (Vesari et al., 1980; Prior et al., 1983).

Althesin has been shown to decrease cerebral oxygen consumption, cerebral blood flow (CBF) and ICP in man (Turner et al., 1973; Sari et al., 1976; Rasmussen, Rosendal and Overgaard, 1978). During the past 5 years it has been used increasingly in Leeds as a first-line agent in the control of increased ICP following severe head injury (Moss et al., 1983), because of its advantage over the barbiturates of rapid elimination (Simpson, 1978). Etomidate has also been in use in several centres for the treatment of severe intracranial hypertension, so that a study of its efficacy is important, especially when its place in intensive care is under critical review for other reasons. A comparative trial of the influence of i.v. infusions of etomidate and Althesin on the control of ICP after severe head injury has been undertaken, and is reported in this communication.

SUMMARY

The increasing use of shorter-acting hypnotic agents to control intracranial pressure (ICP) following severe head injury has prompted a prospective double-blind controlled trial comparing the efficacy of etomidate and Althesin, given by i.v. infusion. Over the dose ranges used, the two drugs appeared equipotent in decreasing ICP whilst preserving cerebral perfusion pressure. However, in two patients (one in each group) ICP did not respond to hypnotic infusion, a feature noted in other studies to occur in a minority of patients. With the cessation of Althesin manufacture and the discussion about the use of etomidate infusions, it is timely to document the effectiveness of etomidate in decreasing ICP.

MATERIALS AND METHODS

Head-injured patients older than 14 years-of-age undergoing intensive care management with full neuromuscular blockade were admitted to the study if a sustained unstimulated increase in mean ICP above 20 mm Hg was recorded for more than 10 min. The 10 patients in this study had suffered severe head injury as indicated by low Glasgow coma scores and increases in ICP (table I). Surface subarachnoid pressure was recorded using the Leeds bolt (Coroneos et al., 1973). Treatment was instituted by commencing an i.v. infusion of either etomidate (five patients) or Althesin (five patients), chosen on a random basis, at a pre-determined rate based on estimated body weight, to a central vein (CV) using an infusion pump. Any patients receiving other drugs known to influence ICP during the infusion period of 70 min were excluded from the study, and no other drugs were given via the CV line during the study. The study comprised one infusion of either etomidate or Althesin in each of 10 patients.

N. M. DEARDEN*, B SC, M B., CH B, F.F A R C S, D. G. McDOWALL, M.D, F.F.A R C S, Department of Anaesthesia, University of Leeds, Leeds, Yorks.

*Present address, for correspondence: Department of Surgical Neurology, Western General Hospital, Crewe Road, Edinburgh EH4 2XU.

TABLE I. *Clinical details, initial ICP and outcome in 10 patients*

	Etomidate	Althesin
Sex	5M	4M:1F
Age (yr)	Mean 27.0 Range 15–44	Mean 27.6 Range 14–45
Glasgow Coma Score on admission	Mode 5 Range 3–7	Mode 5 Range 3–7
Brain swelling	2	1
Intracerebral haematoma	1	1
Subdural haematoma	2	3
Initial ICP (mm Hg)	Mean 23.0 SEM ±2.4	Mean 24.1 SEM ±2.3
Outcome after 1 year:		
Dead/Vegetative	2	3
Severely disabled	0	1
Moderately disabled/ good recovery	3	1

The infusate was dispensed by the Pharmacy, in containers with concealed labels to prevent identification by the medical staff, as undiluted Althesin or etomidate in a concentration of 6 mg ml^{-1} in 5% dextrose. The infusion rates are shown in table II.

The dose regimen was based on the literature available for the two agents when used to produce anaesthesia, sedation and reduction of ICP, and our own previous experiences with the two agents in an ICP reducing role (Ramsay et al., 1974; Savege et al., 1975; Kay, 1976; Popescu, 1976; Sari et al., 1976; Jago and Restall, 1977; Van Hamme, Ghoneim and Ambre, 1978; Sear and Prys-Roberts, 1979; Zattoni et al., 1980; Boys et al., 1981; Ransom, 1981; de Ruiter et al., 1981).

Based on the pharmacokinetic studies of Sear and Prys-Roberts (1979) in the case of Althesin, the above regimen should provide steady-state plasma concentrations at 30, 50 and 70 min. Furthermore, analysis of Ransom's paper (1981) would suggest that a steady-state plasma concentration of etomidate might be reached at 30 min, although the more recent work of Hebron and co-workers (1983) would refute this.

TABLE II. *Infusion rates of Althesin and etomidate*

		Equivalent to:	
Time	Infusion rate	Althesin	Etomidate
0–10 min	$0.5\ \text{ml kg}^{-1}\ \text{h}^{-1}$	$0.5\ \text{ml kg}^{-1}\ \text{h}^{-1}$	$50\ \mu\text{g kg}^{-1}\ \text{min}^{-1}$
10–30 min	$0.2\ \text{ml kg}^{-1}\ \text{h}^{-1}$	$0.2\ \text{ml kg}^{-1}\ \text{h}^{-1}$	$20\ \mu\text{g kg}^{-1}\ \text{min}^{-1}$
30–50 min	$0.3\ \text{ml kg}^{-1}\ \text{h}^{-1}$	$0.3\ \text{ml kg}^{-1}\ \text{h}^{-1}$	$30\ \mu\text{g kg}^{-1}\ \text{min}^{-1}$
50–70 min	$0.4\ \text{ml kg}^{-1}\ \text{h}^{-1}$	$0.4\ \text{ml kg}^{-1}\ \text{h}^{-1}$	$40\ \mu\text{g kg}^{-1}\ \text{min}^{-1}$

TABLE III. *Blood-gas tensions (mean ± SEM) a the start of hypnotic infusion*

	Etomidate	Althesin
Pa_{CO_2} (kPa)	3.9±0.41	3.7±0.29
Pa_{O_2} (kPa)	18.6±1.4	17.9±1.7

During the 70-min study period the following measurements were made: arterial pressure (AP) either directly from the radial artery or indirectly (Automatic BP Monitor, Electrical Medical Equipment, Brighton) to provide both systolic and diastolic pressures at 5-min intervals. Mean arterial pressure was calculated later as diastolic + 1/3 (systolic – diastolic pressure). Good correlation between "Dinamap" and direct arterial pressure readings has been confirmed by Hutton, Dye and Prys-Roberts (1984). ICP was displayed throughout the study on a chart recorder and measurements of mean ICP, taken as the mid-point of the trace width, were made at 5-min intervals. The validity of the ICP measurements was verified using an infusion test (Dearden, McDowall and Gibson, 1984). Blood-gas tensions were obtained at the beginning of the infusion and are given in table III.

Central and peripheral temperatures and central venous pressure (CVP) were measured at the start and end of each infusion. Crystalloid maintenance fluids were administered at a rate equal to the urine output for the previous hour plus 30 ml, to a maximum of 150 ml h^{-1}. CVP measured at mid-axillary level was maintained between +3 and +10 cm H_2O (on IPPV) using colloid, when necessary.

Pupillary reactions were recorded at the start of the study and at 10, 30, 50 and 70 min. Monitoring of cerebral function (CFM) was undertaken in all patients (although two traces in each group were of poor quality).

Differences between the groups were tested by unpaired Student's *t* test, with values of *P* less than 0.05 being considered significant. In all figures $n = 5$ except where stated.

RESULTS

Intracranial pressure

ICP decreased progressively during the infusion in four out of five patients in each group. Seventy five per cent of the mean decrease in ICP occurred during the first 10 min of the Althesin infusion, while only 54% of the total mean decrease in ICP occurred during this period with etomidate. There was a significant percentage reduction in ICP in the etomidate group at 10 and 30 min, and in the Althesin group at 30, 50 and 70 min (fig. 1). Using absolute mean values, the decrease in ICP reached statistical significance at all times only when the data from the etomidate and Althesin groups were combined.

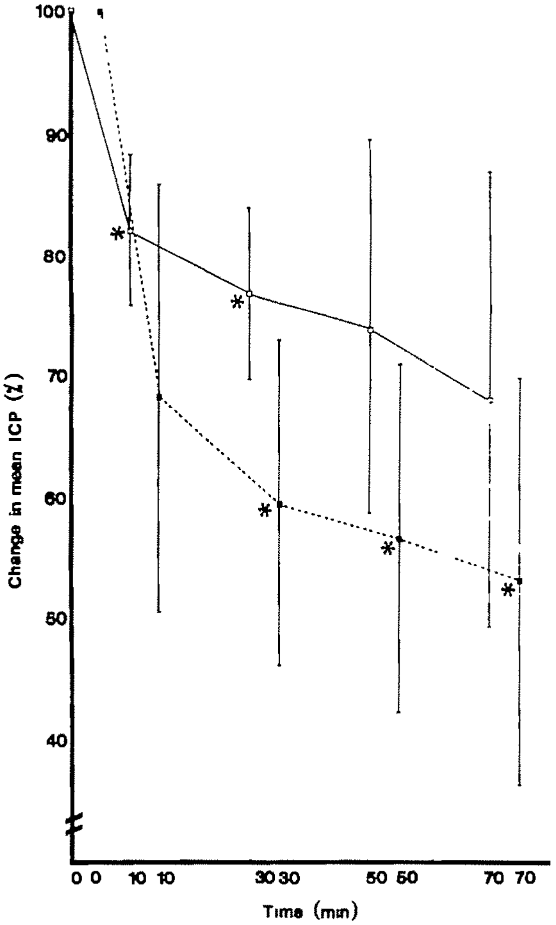

FIG. 1. Percentage alteration in mean ICP (± SEM) against time in etomidate (——) and Althesin (---) groups. *0.05 $P > 0.02$.

If the two non-responder patients, one in each drug group, are excluded, there was a significant correlation between initial mean ICP and the absolute reduction in ICP at 30, 50 and 70 min for both drugs (fig. 2). Variations in the amplitude of the ICP with pulse pressure and artificial respiration were reduced equally by the two drugs, and in proportion to the change in mean ICP (fig. 3).

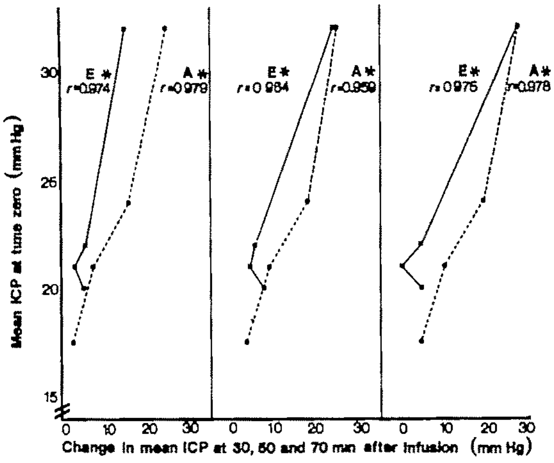

FIG. 2. Mean ICP at time zero correlated with change in mean ICP at 30, 50 and 70 min respectively, for each of the four responsive patients in the etomidate (——) and Althesin (....) groups. *0.05 $> P > 0.02$.

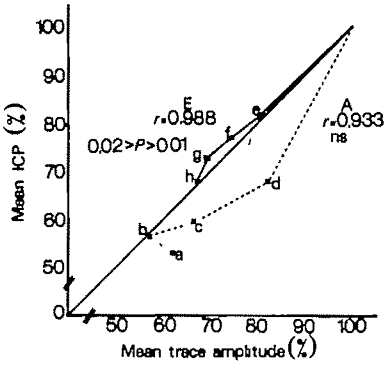

FIG. 3. Mean ICP compared with mean trace amplitude in etomidate (——) and Althesin (---) groups. a = 70 min; b = 50 min; c = 30 min; d = 10 min; e = 10 min; f = 30 min; g = 50 min; h = 70 min (four patients).

Arterial pressure

The baseline values of arterial pressure were slightly higher in the etomidate group, but the difference was not significant. No difference in the state of hydration of the two groups was apparent from analyses of temperature, fluid balance and CVP. Both systolic and mean arterial pressures decreased during the infusion. Mean arterial pressure decreased by 11% with Althesin and by 9.5% with etomidate during the first 10 min, the decreases reaching statistical significance in the etomidate group at 10 and 50 min for systolic and at 50 min for mean arterial pressure. At no time was the decrease in systolic or mean pressure significant in the Althesin group. Combination of the etomidate and Althesin data results in a significant decrease in both mean and systolic arterial pressures at all times. There was statistically no difference in the decrease in arterial pressure between the two groups (fig. 4).

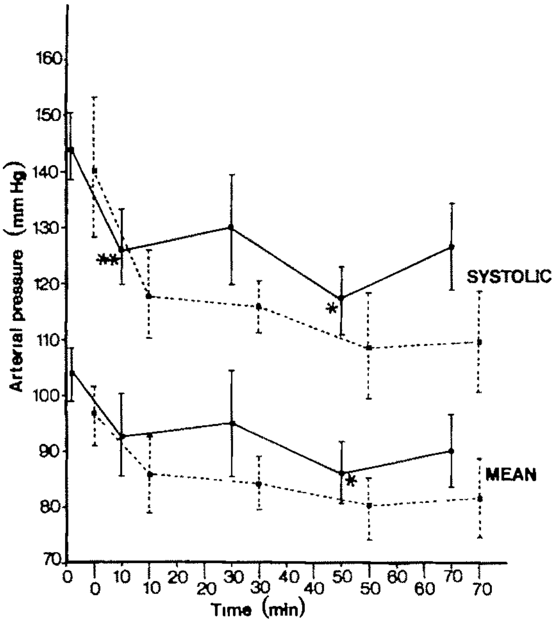

FIG. 4. Systolic and mean arterial pressures (±SEM) against time for etomidate (——) and Althesin (----) groups. *0.05 > P > 0.02; **0.02 > P > 0.01.

There was no correlation between change in mean arterial pressure and in mean ICP with drug administration, except in one patient in each group. In general arterial pressure decreased more than ICP, but the lack of correlation in most patients might indicate that other factors are important in the reduction of the ICP.

Cerebral perfusion pressure

Cerebral perfusion pressure (CPP) (mean AP − mean ICP) decreased to less than 60 mm Hg in one patient in the etomidate group (at 50 min in patient No. 5, whose ICP did not respond to the infusion) and in two patients in the Althesin group (at 30, 50 and 70 min in patient No.4 and at 50 min in patient No. 5, whose ICP was also non-responsive). On the other hand, in one patient in the Althesin group, an initially low CPP of 45 mm Hg increased to 81 mm Hg at 10 min. Although mean CPP appears reduced at all times in both groups, the differences did not reach statistical significance even when data from both groups were combined. Furthermore, there were no statistically significant differences between CPP of the groups at any time (fig. 5).

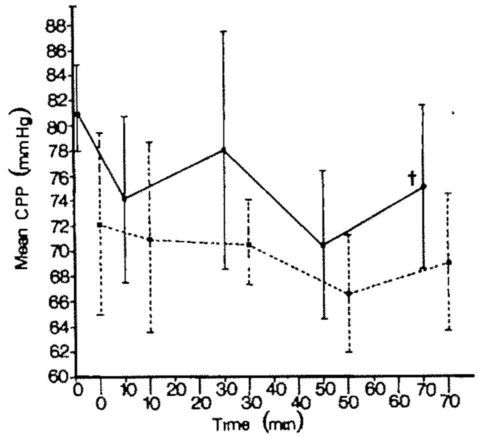

FIG 5. Effect of etomidate (——) and Althesin (----) infusions on mean cerebral perfusion pressure (±SEM). †Four patients.

Heart rate

The heart rate (HR) was slightly faster in the Althesin group at the start of the study, but the difference was not significant. HR increased by 9.5% with etomidate and by 14% with Althesin during the first 10 min of the infusion. Increases in HR in both groups appear dose-related and reach statistical significance at 10, 30 and 70 min in the etomidate group, and at 10, 50 and 70 min in the Althesin group (fig. 6). Although increases in HR are consistently higher in the Althesin group, no statistically significant difference in heart rate was reached at any time between the two groups.

Temperature

There was no change in rectal temperature during the study.

Pupils

Although there was a tendency for pupillary reactions to become sluggish during the infusion, no consistent change was noted in pupillary size, and no obvious differences emerged between the two agents.

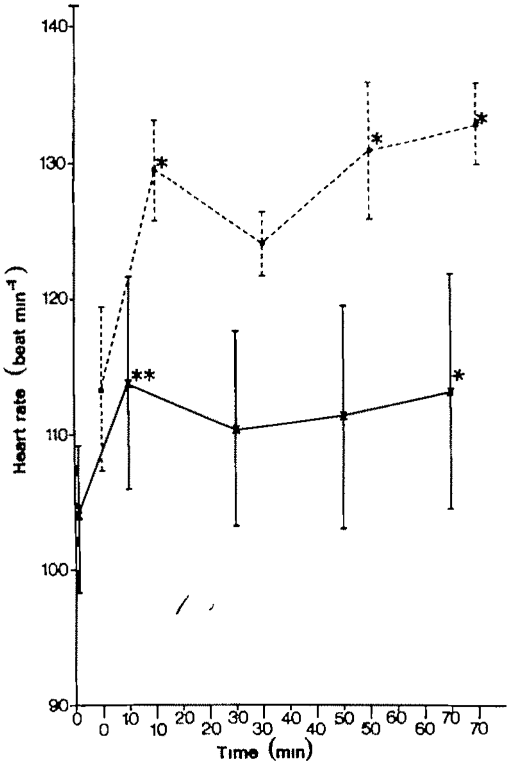

FIG 6. Mean heart rate (±SEM) during etomidate (——) and Althesin (---) infusions. *$0.05 > P > 0.02$; **$0.02 > P > 0.01$.

Cerebral function monitoring

There were inadequate data to compare the two agents, but both infusions appeared to depress the lower border of the cerebral function monitor (CFM) trace with time. These observations are consistent with the reports of Prior, Maynard and Brierley (1978) and Frank and colleagues (1982) for Althesin, and Doenicke and co-workers (1982) for etomidate.

DISCUSSION

The introduction of infusions of hypnotic drugs in the treatment of post-traumatic increases in ICP in an effort to minimize secondary brain damage, has led to a search for agents with a shorter duration of action and fewer side effects than the barbiturates. It is well established that Althesin and etomidate decrease ICP (Pickerodt et al., 1972; Takahashi et al., 1973; Turner et al., 1973; Schulte am Esch, Pfeifer and Thiemig, 1978; Moss et al., 1979; Zattoni et al., 1980; Prior et al., 1983). The mechanism is probably via a reduction in cerebral metabolism and thus CBF (Pickerodt et al., 1972; Van Aken and Rolly, 1976; Sari et al., 1976; Rasmussen, Rosendal and Overgaard, 1978; Renou et al., 1978). The fact that the decrease in ICP correlated poorly with the change in arterial pressure in this study would be consistent with this hypothesis.

Althesin has, however, several disadvantages, including the relatively high incidence of allergic reactions (Beamish and Brown, 1981; Clarke, 1982) and the potential hazards of larger doses of the solubilizing agent Cremophor EL (Knell, Turner and Chambers, 1983; Lawler, McHutchon and Bamber, 1983). Furthermore, during continuous infusion anaesthesia, Althesin appears to induce a more marked derangement of hepatic enzyme activity than do either etomidate or thiopentone (Blunnie et al., 181). These problems have led to the discontinuance of the manufacture of Althesin. This study was conducted before the decision to cease manufacture, but we believe that Althesin provides a well-accepted standard with which to compare the action of other agents. In contrast, etomidate is reported to provide greater cardiovascular stability than Althesin (Popescu, 1976) and does not release histamine (Doenicke et al., 1973). It is a potent anticonvulsant, and has been shown to undergo rapid elimination (Kay, 1976). In addition, the solubilization of 125 mg of the drug in 1 ml of alcohol avoids the administration of Cremophor.

In this study both agents appeared to decrease ICP to the same degree. The failure to reach statistical significance at certain times probably reflects the small sample size and the fact that one patient in each group failed to respond to the treatment. In a series of 48 patients (unpublished data) treated in Leeds with Althesin infusions for increases in ICP after severe head injury, seven were unresponsive. Prior and colleagues (1983) reported that two out of 10 patients failed to respond to an etomidate infusion of up to 25 $\mu g\ kg^{-1}\ min^{-1}$. Both unresponsive patients in their series and in this study had subdural haematomas with associated cerebral oedema.

The shape of the intracranial compliance curve might lead one to anticipate that the decrease in ICP should relate to the initial ICP, and this proved to be the case in this study, as in other previous reports with etomidate (Moss et al., 1979; Prior et al., 1983) and Althesin (Turner et al., 1973).

Preservation of CPP as demonstrated for both agents is in accord with previous results: Sari and colleagues (1976) using Althesin 0.1-mg kg^{-1} bolus followed by 0.3-ml $kg^{-1}\ h^{-1}$ infusion; Moss and colleagues (1979) using etomidate 0.3-ml kg^{-1} boluses;

Schulte am Esch, Pfeifer and Thiemig (1978) using 0.3-ml kg^{-1} boluses of etomidate, and Prior and co-workers (1983) using 0.2-mg kg^{-1} boluses of etomidate. In the current study, CPP was maintained at greater than 60 mm Hg in most patients, in spite of the decreases in mean arterial pressure induced by both agents. The lowest recorded CPP in the Althesin group was 45 mm Hg and in the etomidate group 57 mm Hg. The fact that CPP increased in one patient in the etomidate group and four patients in the Althesin group at some time during the infusion is further supporting evidence that the reduction in ICP was not simply a result of decreases in arterial pressure.

The reduction in both mean and systolic arterial pressures reported in this study is in contrast to the observations of Sari and co-workers (1976), who reported preservation of arterial pressure with Althesin 0.1-ml kg^{-1} boluses followed by an infusion of 0.3 ml kg^{-1} h^{-1} and of Schulte am Esch, Pfeifer and Thiemig (1978) who described the maintenance of arterial pressure following 0.3-mg kg^{-1} boluses of etomidate. However, Turner and colleagues (1973) and Moss and co-workers (1979) reported transient decreases in arterial pressure significant at 3 and 4 min following 0.2-mg kg^{-1} boluses of etomidate. In reviewing 24 papers dealing with the cardiovascular effects of Althesin and etomidate, Lamalle (1976) reported an apparently dose-independent response to etomidate boluses from no change to a 20% reduction in arterial pressure. In contrast, Althesin appears to produce a more dose-related decrease in pressure of between 10 and 20%. Popescu (1976) reported reductions of 1.4% and 3.1% for etomidate (0.19-mg kg^{-1} boluses) and Althesin (0.0523-ml kg^{-1} boluses), respectively, with the reduction in arterial pressure associated with Althesin being significantly greater than that with etomidate. It seems likely that variations between reports depend on differences in dose, state of hydration, degree of sedation and analgesia, and methods of anaesthesia used in the subjects studied. In the present report where observations of CVP, patient temperature and fluid balance indicated that the subjects were normovolaemic, we were unable to show any difference in the degree of change in arterial pressure with the two agents infused in the described dosages.

Our finding of increases in heart rate with both drugs is in agreement with most of the literature. Lamalle (1976) reported increases in heart rate of 30% and 11% 2 min after bolus doses of Althesin 0.07 ml kg^{-1} and etomidate 0.15 mg kg^{-1}. However, Popescu (1976), in a comparative study of etomidate 0.19 mg kg^{-1} and Althesin 0.523 ml kg^{-1} given as boluses, reported a 2.75% reduction in HR with etomidate and a 21% increase in HR with Althesin.

CONCLUSIONS

In conclusions, this prospective, randomized, double-blind trial has demonstrated that both etomidate and Althesin infusions decrease ICP following severe head injury to a similar degree. Both agents reduce systolic and mean arterial pressures in normovolaemic patients, but CPP is little changed. HR increases significantly with both agents—apparently in relation to dose.

It appears that etomidate provides an effective alternative to Althesin in the treatment of increases in ICP following severe head injury at an initial infusion rate of 50 μg kg^{-1} min^{-1} for 10 min (to provide a loading dose) and then of 20–40 μg kg^{-1} min^{-1}. If ICP is not controlled with this dose range, an alternative or additional agent should probably be used.

In Britain, the continuing use of infusions of etomidate in intensive care is under review at the time of writing, following the reports of Allolio and colleagues (1983), Fellows, Byrne and Allison (1983), Fellows and colleagues (1983), Ledingham and Watt (1983), and Sebel, Verghese and Makin (1983) on the effects of the drug on adrenocortical secretion. However, the drug does have certain advantages in that it is associated with cardiovascular stability and possesses anticonvulsant activity. In addition, as demonstrated here, etomidate decreases ICP as effectively as does Althesin. Since the study was completed, the manufacture of Althesin has been discontinued because of concern about anaphylactoid reactions. None-the-less, withdrawal is so recent that the drug provides a useful and familiar yardstick of comparison in respect of controlling ICP following head injury (McIlhany et al., 1983; Moss et al., 1983). Certainly, an hypnotic drug to control ICP is needed—other than the barbiturates, which are associated with circulatory depression and delayed excretion (Krier et al., 1984; Miller et al., 1984). If the problems of adrenocortical suppression can be resolved, perhaps through the use of steroid supplements (Reis Miranda and Stoutenbeek, 1983), then etomidate may have a role in the management of severe head injury.

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USE OF A CONTINUOUS INFUSION OF ALTHESIN IN NEUROANAESTHESIA

Changes in Cerebral Blood Flow, Cerebral Metabolism, the EEG and Plasma Alphaxalone Concentration

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SUMMARY

Ten patients with small supratentorial tumours were studied during craniotomy. Cerebral blood flow (CBF) was measured in the contralateral hemisphere by a modification of the Kety and Schmidt technique using xenon-133 i.v. With an Althesin infusion rate of 0.2 ml kg^{-1} h^{-1}, CBF was 24.4 ± 5.4 ml min^{-1}/100 g and $CMRo_2$ 1.87 ± 0.44 ml min^{-1}/100 g at Pa_{CO_2} 4.1 ± 0.7 kPa (mean ± SD). During constant infusion rates of Althesin, steady values of $CMRo_2$ were obtained, while an increase in infusion rate of 150% was associated with an increase in plasma alphaxalone concentration, a decrease in $CMRo_2$ and a tendency of further EEG suppression. However, great inter- and intraindividual variations were present, and correlations between $CMRo_2$, EEG activity and plasma alphaxalone concentration were weak.

Several i.v. anaesthetic agents are known to depress the cerebral metabolic rate for oxygen ($CMRo_2$) and cerebral blood flow (CBF). Barbiturates, for example, cause a suppression of synaptic transmission and corresponding decreases in blood flow and metabolism. The suppression is dose-dependent until the point of appearance of an isoelectric EEG—corresponding to cessation of synaptic transmission (Michenfelder, 1974; Nilsson and Siesjö, 1975; Astrup, Møller Sørensen and Rahbek Sørensen, 1981). Likewise, Althesin can depress $CMRo_2$ and CBF in man following either bolus injection or during continuous infusion (Sari et al., 1976; Rasmussen, Rosendal and Overgaard, 1978). The purpose of this study was to depress $CMRo_2$ significantly, and to investigate possible correlations between $CMRo_2$, EEG and plasma alphaxalone concentrations.

PATIENTS AND METHODS

Patients

Ten patients (five males; mean age 59 yr, range 37–75 yr; mean weight 74 kg, range 50–94 kg) with cerebral tumours were investigated. They all gave informed consent and the study was approved by the local scientific ethics committee. Selection of patients was undertaken to include those with a midline shift of less than 10 mm, as judged from either CT scanning or arteriography. All tumours were located supratentorially. Before the induction of anaesthesia, all patients were awake, ASA group I–II and were receiving treatment with steroids.

Anaesthesia

One hour before the induction of anaesthesia the patients were premedicated with pentobarbitone 2 mg kg^{-1} i.m., and mepyramine 50 mg i.m. and cimetidine 400 mg by mouth. After preoxygenation, anaesthesia was induced with an infusion of Althesin at a rate of 1.0 ml kg^{-1} h^{-1} and fentanyl 0.2 mg i.v. Pancuronium 0.10–0.15 mg kg^{-1} was given to produce neuromuscular blockade, manual hyperventilation was applied and tracheal intubation performed. From the point of intubation until the end of the first CBF measurement, the anaesthesia was maintained with a continuous infusion of Althesin 0.2 ml kg^{-1} h^{-1}, 66% nitrous oxide in oxy-

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gen and fentanyl in doses of 0.1 mg (total 7.8 ± 2.8 μg kg^{-1} (mean ± SD)). In five patients the rate of infusion of Althesin was 0.2 ml kg^{-1} h^{-1} throughout the study, and CBF was measured on two occasions. In four patients the Althesin infusion rate was increased to 0.5 ml kg^{-1} h^{-1} 30 min before the second CBF determination. In one patient (No. 10, table I) the infusion of Althesin was unintentionally disrupted 30 min before the second CBF measurement. Ventilation was controlled throughout (Servo 900 B) and end-expiratory carbon dioxide concentration monitored.

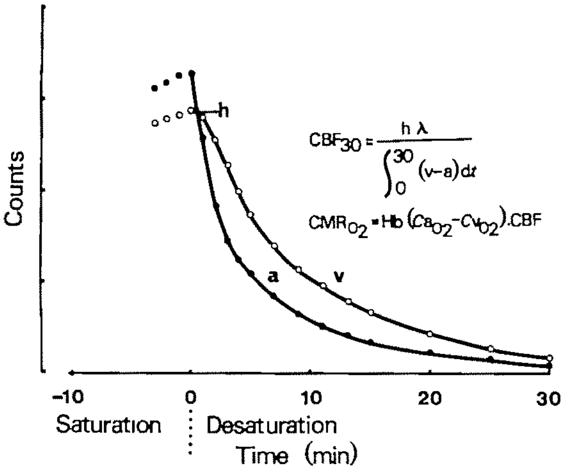

FIG 1. The Kety and Schmidt technique of measuring cerebral blood flow from the xenon-133 desaturation curves obtained by sampling of arterial (a) and internal jugular venous (v) blood and using the "Height (h)-over-Area" formula.

Measurements of CBF, $CMRO_2$ and EEG

The internal jugular vein contralateral to the tumour was cannulated percutaneously using the anterior approach, and a catheter placed at the base of the skull. The position of the catheter was confirmed radiologically. Xenon-133 2 mCi in saline was infused i.v. over a period of 20 min to obtain saturation. Blood samples (2 ml precisely) were drawn using disposable syringes from arterial and jugular venous blood at exact time intervals of 18, 19 and 20 min during saturation and at 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 20, 25 and 30 min during desaturation. Radioactivity in the samples was counted, and the arterial and venous desaturation curves drawn (fig. 1). The amount of xenon-133 released by the brain during the 30-min desaturation period was estimated by planimetry as the area between the arterial and venous desaturation curves. CBF was calculated using the "Height-over-Area" formula (CBF_{30}) and cerebral metabolic rate of oxygen ($CMRO_2$) from the product of CBF and the arterio-venous oxygen difference (Kety and Schmidt, 1948; Lassen and Klee, 1965; Astrup et al., 1984). The partition coefficient for brain tissue was corrected for haemoglobin concentration (Veall and Mallet, 1965). The first CBF measurement was performed about 1 h after the induction of anaesthesia, and the second approximately 1 h later. At least 30 min was allowed to elapse after the increase in the Althesin infusion rate before xenon-133 desaturation and hence the CBF and $CMRO_2$ measurements.

After the induction of anaesthesia, eight EEG electrodes were positioned over the frontal, temporal and occipital regions on the side contralateral to the craniotomy. A 2-min EEG recording was obtained during each xenon-133 desaturation period, while surgery was discontinued to avoid electrical interference with the recording. The EEG recordings were compared with the preoperative EEG and analysed as described by Prior, Maynard and Brierley (1978), using a six-point scale. Level one corresponded to continuous background activity of fairly constant voltage with any combinations of frequency, but without periods of either partial or total suppression. Level two: periods of less than 1 s total or subtotal suppression, separated by bursts of activity usually of 100–300 μV. Level three: periods of 1–3 s duration of total, occasional subtotal suppression, separated by bursts of activity of 100–300 μV. Level four: periods of at least 3 s total suppression separated by bursts of activity usually of 50–100 μV. Level five: periods of at least 3 s total suppression separated by very brief bursts of low voltage less than 50 μV. Level six: no evidence of any cerebral electrical activity even with high gain. This scale, although initially designed for animal experiments with extradurally-placed electrodes, has subsequently been applied in man during the infusion of Althesin (Henderson, McGeorge and Teasdale, 1982).

Assay for alphaxalone in plasma

These analyses were performed at Glaxo Group, Research Limited, Greenford, Middlesex. Plasma alphaxalone was analysed in peripheral arterial blood sampled during each CBF measurement at the time of the EEG recording; plasma was stored at −25°C until assayed.

Plasma, to which internal standard (2β-n-butoxy, 3α-hydroxy-5α-pregnane-11, 20-dione 1 μg) had been added, was buffered to pH 11.4 and extracted with ether. The extract was evaporated to dryness and then derivatized with heptafluorobutyrylimidazole in toluene (10 min 55 °C).

Excess reagent was removed by washing with buffer (pH 7.4). The derivative was diluted with toluene before gas–liquid chromatography (GLC) on 2% Dexsil 300 at 245 °C. Detection was by ECD, and quantitation was by the peak – height ratio method. Assay sensitivity was 20 ng ml^{-1} provided a rigorous conditioning procedure was applied to the GLC column before use. This involved injections of 2, 4-pentanedione and Silyl-8 onto the column at 250 °C and subsequent overnight heating at 290 °C.

Arterial pressure was monitored and the mean pressure (MAP) recorded continuously, as was rectal temperature. Arterial blood-gas analyses were performed twice during each CBF measurement (ABL 1: Radiometer). The oxygen saturations of arterial and jugular venous blood were measured in duplicate (OSM2: Radiometer).

Statistical analyses

The results are indicated as mean ± standard deviation (SD). $P < 0.05$ indicates level of significance. The Mann–Whitney test was used for unpaired data; Student's t test for paired data. Linear regression and correlation coefficients were used for correlations between two variables.

RESULTS

During the first CBF study at an Althesin infusion rate of 0.02 ml kg^{-1} h^{-1} ($n = 10$), CBF was 24.4 ± 5.4 ml min^{-1}/100 g and $CMRO_2$ 1.87 ± 0.44 ml min^{-1}/100 g at Pa_{CO_2} 4.1 ± 0.7 kPa and body temperature 35.7 ± 0.4 °C.

In five studies at an unchanged infusion rate of 0.2 ml kg^{-1} h^{-1}, the changes in CBF and $CMRO_2$ were from 21.8 ± 5.0 to 20.0 ± 6.4 ml min^{-1}/100 g and from 1.84 ± 0.20 to 1.88 ±0.80 ml min^{-1}/100 g, respectively (table I). During the second CBF measurement (infusion rate 0.5 ml kg^{-1} h^{-1} (patients Nos 6–9, table I)) CBF decreased from 25.0 ± 5.7 to 20.1 ± 8.6 ml min^{-1}/100 g and $CMRO_2$ from 1.85 ± 0.71 to 1.50 ± 0.30 ml min^{-1}/100 g. The decrease in $CMRO_2$ was greater than 15% in three patients while a small increase was found in one patient. In one

TABLE I *EEG levels (Prior, Maynard and Brierley, 1978), plasma alphaxalone concentrations (µg ml^{-1}), CBF (ml min^{-1}/100 g), and $CMRO_2$ (ml min^{-1}/100 g) in 10 patients with cerebral tumours anaesthetised with a continuous infusion of Althesin 0.2, 0.5 or 0.0 ml kg^{-1} h^{-1} supplemented with nitrous oxide and fentanyl. Central temperatures, mean arterial pressures (MAP) and Pa_{CO_2} are indicated*

Patient No.	Althesin infusion rate (ml kg^{-1} h^{-1})	Central temp. (°C)	Arterial pressure (MAP) (kPa)	Pa_{CO_2} (kPa)	EEG level	Plasma alphaxalone concn (µg ml^{-1})	CBF (ml min^{-1}/100 g)	$CMRO_2$ (ml min^{-1}/100 g)
1	0.2	36.1	15 3	3.7	3–4	2.19	28	1.9
	0.2	36.9	13.3	3.5	3–4	2.80	16	0 9
2	0.2	35 8	11 5	3.9	2	2.36	25	2.1
	0.2	35.6	11.1	4 1	1	2.43	31	3.1
3	0 2	35.6	12 9	3.9	5	2.25	15	1.7
	0.2	35.2	13.1	3.5	5	2.36	15	1.8
4	0.2	35.4	15.1	5.0	5	3.05	22	1.9
	0.2	35.3	13 3	2.5	4	2.19	20	1.8
5	0.2	35.9	14.0	4.5	1	3.44	19	1.6
	0.2	35.9	10.2	4 6	1	1.51	18	1.8
6	0 2	36.0	10.6	3 9	1	2 01	31	1 8
	0 5	35.6	10.0	3.9	4–5	3.64	33	1.5
7	0.2	36.3	13 3	3.9	3	1.50	21	2.1
	0.5	36.0	11.1	3 7	5	2.47	15	1.4
8	0.2	35.4	11.1	5.2	1	2.38	31	2 6
	0.5	35 3	10 6	4.6	1	7.53	18	1.9
9	0.2	35.7	16 0	3.1	3	3.65	23	0.9
	0.5	35.5	14.2	2.8	3	3.97	15	1.2
10	0.2	35.1	14.6	3.6	1	2.98	29	2 1
	0.0	35.0	16.4	3.5	1	0.49	32	2.5

patient, an interruption to the Althesin infusion was associated with an increase in $CMRO_2$ (patient No. 10, table I).

The changes in the EEG, and the correlations between $CMRO_2$ and EEG values are shown in figure 2. As indicated, $CMRO_2$ never decreased below 1.6 ml min^{-1}/100 g at EEG level 1, and $CMRO_2$ did not surpass 2.1 ml if EEG traces were level 3 or more. In three patients a decrease in $CMRO_2$ was associated with suppression of EEG activity. In six patients a decrease in $CMRO_2$ was observed while the EEG level was unchanged, and in one patient suppression of EEG activity was found with an unchanged $CMRO_2$.

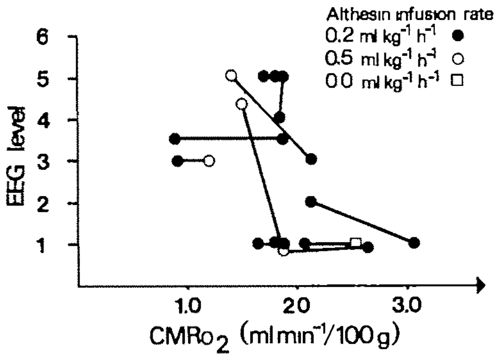

FIG 2. Relationship between changes in $CMRO_2$ (ml min^{-1}/100 g) and EEG level (as described by Prior, Maynard and Brierley (1978)). $CMRO_2$ and EEG were measured on the contralateral hemisphere during craniotomy for cerebral tumor.

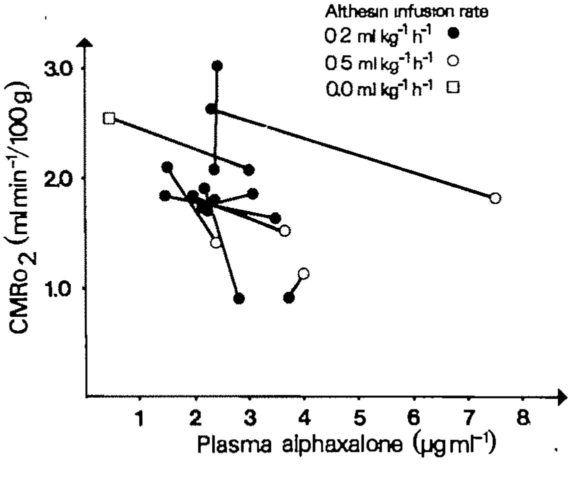

FIG 3. Relationship between changes in plasma alphaxalone concentration (μg ml^{-1}) and $CMRO_2$ (ml min^{-1}/100 g) measured on the contralateral hemisphere during craniotomy for cerebal tumour.

The correlations between corresponding values of plasma alphaxalone and $CMRO_2$ are shown in figure 3. In six patients, an increase in plasma alphaxalone was associated with a decrease in $CMRO_2$; in three patients with an increase in $CMRO_2$; in one patient, unchanged plasma alphaxalone concentration was observed at two different values of $CMRO_2$. As in figure 2, great inter- and intraindividual differences in the relationship was found. In total (n = 20) the correlation between plasma alphaxalone concentration and $CMRO_2$ was insignificant.

The relationship between changes in plasma alphaxalone concentration and EEG level is shown in figure 4. Again, great inter- and intraindividual differences were observed. In only three patients was an increase in plasma alphaxalone concentration associated with a suppression of EEG activity; in six patients unchanged EEG activity was observed at different alphaxalone concentrations and in one patient a suppression of EEG activity was associated with unchanged plasma alphaxalone concentration.

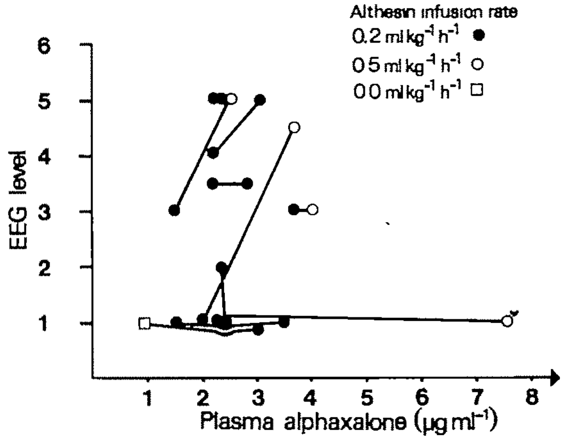

FIG. 4. Relationship between changes in plasma alphaxalone concentration (μg ml^{-1}) and EEG level. EEG was obtained from the contralateral hemisphere during craniotomy for cerebral tumour.

The increase in infusion rate was associated with a decrease in EEG activity in two patients, and an unchanged level in two other patients. A decrease in $CMRO_2$ was observed in three of four patients, and an increase in plasma alphaxalone concentration in all four patients (table I).

DISCUSSION

The method used in this study to measure CBF and $CMRO_2$ is a modification of the inhalation method described by Kety and Schmidt (1948). We measured CBF in the contralateral hemisphere of the tumour because regional flow differences usually seen in cerebral hemisphere with tumours (Pálvölgyi, 1969) would invalidate the result of hemispheric studies. The effect of the tumour on CBF and CMRO$_2$ in the contralateral hemisphere is not known, but by restricting the measurements to patients who were fully alert before surgery and showing only a moderate mass effect of the tumour, the influence of the contralateral hemisphere was assumed to be minimal. Therefore, we assumed that intracranial pressure in the contralateral hemisphere was low and would only influence the cerebral circulation and metabolism to a minor degree. In a recent study of CBF and CMRO$_2$ in awake unpremedicated patients with supratentorial tumours, we used the i.v. modification of Kety and Schmidt as described in the present study, and obtained CBF values of 47 ml min^{-1}/100 g and CMRO$_2$ of 3.3 ml min^{-1}/100 g (Astrup et al., 1984). These values correspond to the values found in normal man (Lassen, 1959), and argue against a major influence of the tumour on the contralateral hemisphere. Nevertheless, methodological errors may occur. These errors include contamination with extracranial blood and blood from the contralateral hemisphere (Lassen, 1959; Lassen and Lane, 1961). Furthermore, contamination by central venous blood also occurs (Murray, Hoschl and Choy, 1978). The last mentioned error is a function of the difference in pressure between central venous blood and the pressure in the jugular bulb, and might be eliminated by keeping the inspiratory pressure as low as possible. In the present study we used a respiratory frequency of about 20 b.p.m., and the inspiratory phase of the respiratory cycle was constant at 30%.

This study presumes that steady-state conditions pertain during the 30-min desaturation period. This assumption was fulfilled as far as Pa_{CO_2} was concerned, but the mean arterial pressure did increase during the operative procedure, especially on incision of the skin. Thus, the nociceptive stimulation induced by the operation might influence the measurements. According to Kuramoto and others (1979), nerve stimulation will increase EEG activity and CMRO$_2$ in anaesthetized dogs. However, in all of the patients the first CBF measurement was commenced before the dura was opened, while the second measurement was performed during the operative evacuation of the tumour. Red cerebral veins have often been seen during craniotomy in patients with cerebral tumours (Feindal and Perot, 1965). This hyperoxygenation of the venous blood can arise suddenly, and is often provoked by the operative procedure. If a hemispheric luxury syndrome does occur (Lassen, 1966) on the tumour site, the high venous oxygen saturation will result in an underestimation of CMRO$_2$ as a result of contamination of the contralateral hemisphere. In the present study this might explain the low values of CMRO$_2$ ($<$ 1.4 ml min^{-1}/100 g) found in three studies of CBF.

The present study indicates that Althesin decreases CBF and CMRO$_2$. This is in accordance with studies in baboons (Pickerodt et al., 1972) and humans (Renou et al., 1976; Sari et al., 1976; Rasmussen, Rosendal and Overgaard, 1978). Sari and colleagues (1976) found CBF values of 29 ml min^{-1}/100 g at Pa_{CO_2} 4.8 kPa during continuous Althesin infusion at a rate of 0.3 ml kg^{-1} h^{-1}. According to Sari and colleagues (1976), cerebral carbon dioxide reactivity is maintained during Althesin anaesthesia, and this might be the explanation for the lower values of CBF in the present study, as Pa_{CO_2} was kept lower. Like Sari and colleagues (1976), we found considerable interindividual variation in CBF and CMRO$_2$. The reason could be methodological errors and difficulties in maintaining steady-state conditions during the measurements. This, together with the restricted number of investigations and a great individual difference in sensitivity to Althesin might explain the lack of correlation between CMRO$_2$, EEG and plasma alphaxalone concentration.

After increasing the infusion rate from 0.2 to 0.5 ml kg^{-1} h^{-1}, we found an increase in plasma alphaxalone concentration in four studies and suppression of EEG activity in only two of four patients. The results confirm the studies by Henderson, McGeorge and Teasdale (1982) who found a correlation between rate of infusion of Althesin and suppression in EEG, and the studies by Frank and colleagues (1982) who found a significant correlation between plasma alphaxalone concentration and cerebral function monitor trace. In addition, our results are a confirmation of the study performed by Sear and Prys-Roberts (1979), who found an almost linear correlation between the rate of infusion of Althesin and plasma alphaxalone concentration. The paradoxical association of increased plasma alphaxalone concentration and increased CMRO$_2$ found in three patients may be caused by methodological errors in the estimation of CMRO$_2$, or absence of steady-state conditions as a result of the operative procedure.

Neuroanaesthesia using a continuous infusion of Althesin produces a dose-dependent decrease in

CBF and CMRO$_2$ with a 50% decrease in CMRO$_2$ at doses of 0.5 ml kg^{-1} h^{-1}. Simultaneously, a pronounced suppression of EEG occurs. However, great interindividual variations are present, and it is not possible to predict the actual value of cerebral oxygen uptake from EEG recordings or plasma alphaxalone concentrations.

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COMPARISON BETWEEN HIGH-DOSE SUFENTANIL–OXYGEN AND HIGH-DOSE FENTANYL–OXYGEN FOR NEUROANAESTHESIA

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High-dose fentanyl–oxygen anaesthesia 100 $\mu g\ kg^{-1}$ can prevent increases in systemic arterial pressure and heart rate in response to the induction of anaesthesia and the stimulation of surgery (Shupak et al., 1983). In addition, the technique is associated with acceptable brain relaxation in patients with intracranial mass lesions. The cautious administration of naloxone following surgery produces immediate awakening, and permits early extubation of the trachea without arterial hypertension or cardiac arrhythmia. However, fentanyl-induced seizures have been observed in animals following the administration of 200–400 $\mu g\ kg^{-1}$ (Carlsson et al., 1982), and in one patient after the rapid administration of fentanyl 20–30 ml i.v. (Rao, Nagaprasadarao and El-Etr, 1982).

Sufentanil, which is 5 to 10 times as potent as fentanyl, has a significantly greater margin of safety when given in large amounts to animals (Neimegeers et al., 1976). Reversal of high-dose sufentanil–oxygen anaesthesia by naloxone should be facilitated because of the shorter half-life of sufentanil compared with fentanyl (Bovill et al., 1981). Thus, sufentanil would appear to be a more suitable high-dose narcotic anaesthetic for neurosurgery than fentanyl. To determine this, we compared the two high-dose narcotic anaesthetics in neurosurgical patients. Following both high-dose narcotic anaesthetics, the efficacy of the postoperative administration of naloxone was assessed according to the total dose required to maintain satisfactory ventilation, the patient's mental status and evidence of residual analgesia.

SUMMARY

The cardiovascular responses to anaesthesia, neurosurgery and the postoperative administration of naloxone were studied in 20 patients. Ten patients were anaesthetized with sufentanil 20 $\mu g\ kg^{-1}$ and 10 with fentanyl 100 $\mu g\ kg^{-1}$, and oxygen. At 30-min intervals, sufentanil 50 μg or fentanyl 250 μg was given to maintain anaesthesia. Mean arterial pressure and heart rate did not increase following intubation, incision of the scalp or infusion of naloxone. Because of inadequate anaesthesia, thiopentone was administered at the end of surgery to one patient who had received sufentanil and seven patients who received fentanyl. Apart from one patient in each group the tracheal tubes were removed within 1 h of the start of the administration of naloxone. Recall of tracheal intubation or surgery was not reported by any patient. High-dose sufentanil–oxygen anaesthesia, like high-dose fentanyl–oxygen anaesthesia, was satisfactory for use in neurosurgery. However, high-dose narcotic anaesthesia, followed by the postoperative administration of naloxone, requires that skilled nursing care be available for many hours after surgery.

PATIENTS AND METHODS

Patients

Twenty patients aged 18–64 yr requiring elective neurosurgical procedures of 3.6 h average duration and without other severe systemic diseases were randomly assigned to receive sufentanil or fentanyl. Approval for this investigation was obtained from

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our institution's Human Studies Committee. Informed consent was obtained from each patient during the preoperative interview. Diazepam 5–10 mg by mouth and atropine 0.4 mg i.m. were given 1.5 h before the induction of anaesthesia.

Induction and maintenance of anaesthesia

In the operating room, a radial artery catheter was inserted to permit the continuous measurement of systemic arterial pressure (AP) and the intermittent assessment of arterial blood-gas tensions (ABG). The alveolar–arterial oxygen tension difference ($P\text{A}_{\text{O}_2}-P\text{a}_{\text{O}_2}$) was calculated by using: $P\text{A}_{\text{O}_2} = P\text{I}_{\text{O}_2} - P\text{a}_{\text{CO}_2}\,[F\text{I}_{\text{O}_2} + (1-F\text{I}_{\text{O}_2})/0.8]$ for $F\text{I}_{\text{O}_2} < 1.0$ (control) and $P\text{A}_{\text{O}_2} = P\text{I}_{\text{O}_2} - P\text{a}_{\text{CO}_2}$ for $F\text{I}_{\text{O}_2} = 1.0$ (intraoperative), and measured $P\text{a}_{\text{CO}_2}$ and $P\text{a}_{\text{O}_2}$. ECG (HR), two-lead EEG, expired carbon dioxide concentrations, depression of twitch response to stimulation of the ulnar nerve, and temperature were monitored during the operation. Blood concentrations of sufentanil or fentanyl were determined at predetermined times. Each sample was centrifuged immediately and the plasma frozen and stored until analysis.

After a period of stabilization and measurement of baseline values, anaesthesia was induced with a continuous infusion of sufentanil or fentanyl i.v. at a rate of 30 μg min^{-1} or 150 μg min^{-1}, respectively, while the patient breathed oxygen by mask. Verbal contact with the patient was maintained until loss of consciousness and ventilation was assisted. After 2 min, the rate of the infusion was increased to 50 μg min^{-1} for sufentanil, and to 250 μg min^{-1} for fentanyl until a total dose of sufentanil 20 μg kg^{-1} or fentanyl 100 μg kg^{-1} had been infused. In addition, tubocurarine 200 μg kg^{-1} and pancuronium 30 μg kg^{-1} were given to facilitate intubation of the trachea (Lebowitz et al., 1980) after patients received sufentanyl 4 μg kg^{-1} or fentanyl 20 μg kg^{-1}. Additional sufentanil or fentanyl (bolus injections of 50 μg or 250 μg i.v., respectively) were administered at 30-min intervals after termination of the infusion. Mechanical ventilation maintained $P\text{a}_{\text{CO}_2}$ near 4.0 kPa. Frusemide 1 mg kg^{-1} was given before craniotomy to six and seven patients who received sufentanil and fentanyl, respectively. Following completion of surgery, neuromuscular blockade was antagonized with neostigmine 3 mg and atropine 1.2 mg. Patients were monitored (AP, HR) and ventilated with oxygen during transport to the neurosurgical intensive care unit.

Postoperative naloxone administration, and evaluation of the anaesthetic

All patients received a bolus injection of naloxone 1.5 μg kg^{-1} i.v., repeated if necessary, until awakening with spontaneous ventilation. Following this, a continuous infusion of naloxone i.v. was begun at a rate of 6–12 μg min^{-1} adjusted to maintain respiratory rate (RR) greater than 12 b.p.m. Cardiovascular indices (AP, HR), RR, and Glasgow Coma Scores (GCS) were recorded frequently and blood concentrations of sufentanil or fentanyl determined on the first and second mornings after surgery. Time to extubation of the trachea after arrival in intensive care and the incidence of arrhythmia, nausea and headache were recorded by nursing staff in the period after operation. Complaints of nausea and vomiting were managed by a decrease in the rate of the naloxone infusion to one-half of the previous setting, with careful monitoring of any simultaneous decreases in RR. If a satisfactory decrease in the rate of the infusion could not be accomplished at that time without compromising respiratory status, prochlorperazine was given i.m. Patient recall was determined by one of the investigators during a postoperative interview which included specific questions concerning the last remembered experience before the induction of anaesthesia, memory of intubation and surgery, and the first memory upon awakening from anaesthesia. Induction of anaesthesia and recovery were evaluated by each patient and their anaesthetist.

Statistical analysis

Characteristics of the patients and the operative techniques were analysed using analysis of variance and Fisher's Exact test. Measurements obtained during operation were evaluated using analysis of the variance between treatment groups and paired *t* tests for special comparisons within groups. Postoperative recovery indices and characteristics of naloxone administration were analysed using analysis of variance and the Kruskal–Wallis Chi-square test. Adverse responses to naloxone administration and overall evaluations of anaesthesia were analysed using Fisher's Exact and Mantel–Haenszel tests, respectively. Statistical significance was indicated by $P < 0.05$.

RESULTS

Before operation

Demographic characteristics of the patients and their operations are shown in table I. The two study groups were similar except for their weights.

TABLE I. *Characteristics of patients receiving high-dose narcotic–oxygen neuroanaesthesia (mean values±SD (or number of patients)).* *$P<0$ *05. ‡Carotid endarterectomy and cervical foramenectomy*

	Sufentanil	Fentanyl
Male/Female	7/3	8/2
Weight (kg)*	82±8	70±11
Age (yr)	49±13	52±16
Craniotomy	8	10
Other procedures	2‡	0
Duration of operation (h)	3.5±1.4	3.6±1.2
Range (h)	1.7–6.2	1.5–5.1
ASA Class		
I	1	1
II	3	4
III	5	5
IV	1	0

During operation

Cardiovascular responses to high-dose sufentanil and high-dose fentanyl–oxygen anaesthesia are presented in table II. After establishment of comparable baseline values in both groups, mean arterial pressure (MAP) followed a smooth course and there were no differences between the groups at any time. The baseline heart rate in the fentanyl group was significantly higher than that in the sufentanil group, and decreased significantly from the baseline value with fentanyl administration. Mean alveolar-to-arterial oxygen gradients (table II) did not differ between groups. Within each group, mean (PA_{O_2} – Pa_{O_2}) did not decrease significantly during the course of the procedure, nor at the end of surgery when compared with values at intubation.

Chest wall rigidity was not observed in any patient during the induction of anaesthesia with either drug. Loss of the eyelash reflex, indicating loss of consciousness, occurred in 4.8 ± 1.8 min and 4.3 ± 1.8 min (mean value ± SD) for patients who received sufentanil and fentanyl, respectively.

EEG recordings displayed an irregular mixture of theta and delta activity characteristic of high-dose narcotic anaesthesia. No abnormal patterns or waves were observed in any patient.

At the conclusion of surgery, some patients exhibited increases in muscle tone, arterial pressure, heart rate and EEG activity during removal of head clamps and bandaging. These episodes of sudden arousal were treated with a dose of thiopentone 3 mg kg^{-1} in seven patients (craniotomy) who received fentanyl, and 5 mg kg^{-1} in one patient who received sufentanil for a carotid endarterectomy lasting 5 h.

Plasma concentrations

Plasma concentrations of sufentanil and fentanyl followed similar time courses (fig. 1). The plasma concentration of fentanyl was 10 ng ml^{-1} near the end of surgery and 0.7 ng ml^{-1} the following morning. Residual sufentanil was not detected in plasma samples obtained following surgery.

TABLE II *Cardiovascular responses and* (PA_{O_2} –Pa_{O_2}) *measured intraoperatively during administration of high-dose narcotic–oxygen neuroanaesthesia (mean values±SEM). †After incision.**$P<0$ *05 compared with control*

	Sufentanil			Fentanyl		
	MAP (mm Hg)	HR (beat min^{-1})	($PA_{O_2} - Pa_{O_2}$) (kPa)	MAP (mm Hg)	HR (beat min^{-1})	($PA_{O_2} - Pa_{O_2}$) (kPa)
Control	94±6	74±6	3.06±0.8	92±10	88±8	2.67±0.53
Intubation	93±6	74±6	31 33±2.4*	90±5	93±10	30.93±1.73*
Incision	88±6	64±2	35.73±4.9*	87±4	71±10	35.47±2.93*
30 min†	93±4	62±3		89±4	75±7	
60 min	91±4	62±3	38.67±3.6*	89±3	72±7	38 67±4 00*
90 min	88±4	63±4		87±4	67±4‡	
120 min	97±5	66±6		90±3	74±5	
150 min	93±6	68±6	35.20±3.9*	87±3	74±5	37.20±3 58*
180 min	99±8	70±9		90±6	73±4	
End surgery	92±4	67±5	36.13±2.9*	92±3	77±4	35.60±2.80*

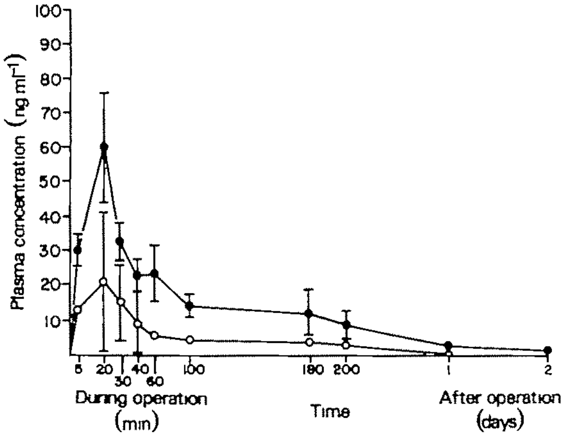

FIG 1. Plasma concentrations of sufentanil (open circles) and fentanyl (closed circles) Each circle represents the mean value ± SD of eight patients.

Postoperative naloxone administration

Characteristics of postoperative naloxone administration following high-dose narcotic neuroanaesthesia are displayed in table III. Six patients who received sufentanil were awake and breathing at a rate of at least 12 b.p.m. after having received an average of three bolus injections of naloxone 1.5 μg kg^{-1} i.v. or a total dose of 379 μg, compared with seven patients who received fentanyl who required an average of one bolus injection i.v. or a total dose of naloxone 116 μg. Recovery times, assessed by the return of the eyelash reflex, response to verbal commands, and attainment of satisfactory ventilatory status including a respiratory rate greater than 12 b.p.m. were not significantly different between the study groups. In all but one patient in each of the groups the trachea was extubated in 29 ± 21 min (sufentanil) and 28 ± 15 min (fentanyl) (mean value ± SD) after admission to the neurosurgical intensive care. No patient in either group required subsequent emergency ventilation or re-intubation of the trachea. However, there was one instance of respiratory depression which required a rapid increase in the rate of the naloxone infusion in a patient who had received sufentanil. The total dose of naloxone administered by i.v. infusion was 4389 ± 2303 μg in 16 ± 4 h for patients who had received sufentanil and 5409 ± 2642 μg in 17 ± 3 h for patients who had received fentanyl (mean value ± SD).

Cardiovascular responses, respiratory rate and GCS during postoperative naloxone administration following high-dose narcotic anaesthesia are shown in table IV. There were no differences between the groups for MAP and heart rate, although MAP was higher than baseline values in both groups. GCS plateaued at values consistent with good neurological recovery after 2 h and reached their highest values after 16 h.

TABLE III. *Characteristics of postoperative naloxone administration following high-dose narcotic-oxygen neuroanaesthesia (mean values±SD).* *P<*0.05*

	Sufentanil	Fentanyl
No. of bolus naxolone administrations*	7±2	4±1
Range	4–9	2–6
Time to extubation (min)	29±21	28±15
Dose of naloxone (μg h^{-1})	340±210	330±140
Total naloxone infused (μg)	4389±2303	5409±2642
Duration of naloxone infusion (h)	16±4	17±3

Side effects of naloxone administration

No agitation or disturbances in cardiac rhythm, requiring pharmacological intervention, were observed in any patient (table V). Nausea, vomiting and headache occurred in approximately half the patients. Those with nausea received prochlorperazine i.m., while those with headache did not require supplementary analgesics.

Evaluation of anaesthesia

Overall evaluations of anaesthesia and recovery made by patients and anaesthetists are presented in table VI. No memory of intubation of the trachea or surgery was reported by any patient during the postoperative interview. One patient who received fentanyl during suboccipital craniectomy for metastatic tumour removal and subsequent ventriculostomy never regained consciousness and died 5 days later. Neurological examination in the period after operation indicated probable brainstem injury as a result of a difficult surgical dissection and manipulation in the posterior fossa.

DISCUSSION

High-dose sufentanil–oxygen anaesthesia maintained acceptable cardiovascular stability by pre-

TABLE IV. *Cardiovascular responses and recovery indices during naloxone administration in the postoperative period following high-dose narcotic–oxygen neuroanaesthesia. *Mean values±SEM; **average values. †After admission to intensive care. ‡Nine of 10 patients in this group were intubated at this time; §Eight of 10 patients in this group were intubated at this time*

	Sufentanil				Fentanyl			
	MAP* (mm Hg)	HR* (beat min^{-1})	RR* (b.p.m)	GCS* (max=15)	MAP (mm Hg)	HR (beat min^{-1})	RR (b.p.m.)	GCS (max=15)
Admission to intensive care	93±6	74±7	‡	7	112±7	89±10	§	10
30 min†	109±7	75±6	12±2	12	112±7	96±10	15±2	11
1 h	109±6	70±5	14±1	12	114±5	93±8	15±1	12
2 h	113±5	76±5	15±2	14	104±3	86±5	17±1	13
4 h	101±4	75±4	17±1	13	103±4	89±4	18±1	12
8 h	97±5	79±6	18±1	14	100±3	88±3	18±1	12
16 h	94±5	81±6	18±1	15	99±3	91±4	18±1	14

venting increases in MAP and HR during intubation and surgical stimulation. The decrease in HR observed during the procedure (in both groups) was probably caused by stimulation of brainstem vagal nuclei by the sufentanil or fentanyl.

Chest wall rigidity was not observed during the induction of anaesthesia, probably because of the early administration of neuromuscular blockers. In a previous investigation, this complication was not observed when pancuronium was infused simultaneously with fentanyl (Hill et al., 1980). However, a 28% frequency of chest wall rigidity was observed in cardiac surgical patients receiving an infusion of sufentanil at a rate of 300 μg min^{-1}, despite pretreatment with pancuronium (deLange et al., 1982). The maximum infusion rate of sufentanil in this investigation was 50 μg min^{-1}.

Pulmonary dysfunction, as manifested by deterioration in arterial oxygenation, was not observed in patients in this study after exposure to 100% oxygen for as long as 6 h. Other signs of oxygen toxicity, not measured in these patients, such as decreases in vital capacity and compliance did not pose clinically significant problems. However, a recent investigation of normal subjects exposed to 95% oxygen for 16.7 h revealed alveolar lavage fluid containing increased protein and inflammatory cell content (Davis et al., 1983). These changes, although reversible, implied that the onset of pulmonary oxygen toxicity may occur at an earlier dose × time interval than was previously believed. Therefore, it would seem prudent to avoid prolonged exposure to a high oxygen concentration by switching to an air–oxygen mixture when feasible during high-dose narcotic anaesthesia.

Sufentanil was considered to be five times as potent as fentanyl in this investigation. The significantly higher frequency of sudden arousal at the end of surgery requiring thiopentone administration in patients who received fentanyl indicated that this

TABLE V. *Number of patients with adverse responses to naloxone administration following high-dose narcotic–oxygen neuroanaesthesia*

	Sufentanil	Fentanyl
Arrhythmias	0	0
Hypertension	0	0
Agitation	0	0
Nausea/vomiting	5	4
Headache	6	5

TABLE VI *Overall evaluations of anaesthesia and recovery. *One fentanyl patient died before extubation as a result of surgical complications unrelated to anaesthesia, and was not included in analysis*

	Sufentanil		Fentanyl	
Evaluation	Induction	Recovery	Induction	Recovery
Patient				
Good	10	10	8	8
Satisfactory	0	0	1	0
Bad	0	0	0	1
Total	10	10	9*	9*
Anaesthetist				
Good	9	10	9	8
Satisfactory	1	0	0	1
Bad	0	0	0	0
Total	10	10	9*	9*

potency ratio may not have been appropriate for this clinical setting. That is, fentanyl 140–170 μg kg^{-1} might have been a better choice than 100 μg kg^{-1} to compare with 20 μg kg^{-1} of sufentanil. This assumption is further supported by the finding that the plasma concentration of fentanyl at the end of surgery was probably below that necessary to preserve unresponsiveness to surgical stimulation (Hug and Moldenhaver, 1982).

Postoperative reversal of high-dose sufentanil–oxygen neuroanaesthesia initially required more bolus naloxone i.v. than did high-dose fentanyl–oxygen neuroanaesthesia. The reason for this finding was unclear. However, the total dose of naloxone administered to patients was not different between study groups. Although it was felt that the shorter half-life of sufentanil would facilitate its reversal by naloxone, this was not found in our study. Although early and sustained neurological recovery allowed the rate of the naloxone infusion to be decreased after 2 h in all patients, it should be emphasized that these patients required the administration of naloxone for many hours after surgery because of the respiratory depression secondary to the presence of residual narcotic (Hug and Murphy, 1979). Therefore, skilled nursing personnel familiar with the hazards associated with this technique were available.

The rapid administration of naloxone 0.2–0.4 mg i.v. has been associated with pulmonary oedema (Flacke, Flacke and Williams, 1977), cardiac arrhythmias (Michaelis et al., 1974), hypertension (Tanaka, 1974), rupture of an intracranial aneurysm (Estilo and Cottrell, 1981) and sudden death (Andree, 1980). In most of these reports, the patients were in pain already, receiving sympathomimetics as supportive therapy for unstable cardiovascular conditions, or just emerging from anaesthesia without proper monitoring during transport. Previous investigations (Hasbrouck, 1971; Johnstone et al., 1974) had indicated that careful administration of naloxone following nitrous oxide–narcotic anaesthesia avoided hypertension and cardiac arrhythmia. A dose of naloxone 1.5 μg kg^{-1} administered as a bolus injection i.v. should not be exceeded, and an appropriate interval, during which effects are observed, should separate repeat injections. The frequencies of headache, nausea and vomiting in this investigation were not different from those in a previous study of patients who received nitrous oxide narcotic–thiopentone neuroanaesthesia without administration of naloxone after operation (Shupak and Harp, 1981).

In summary, the smooth induction and intraoperative course characteristic of high-dose narcotic anaesthesia was observed in this investigatin of neurosurgical patients. The difference in anaesthetic effect observed at the end of surgery in the two study groups was probably related to the doses of sufentanil and fentanyl used. Safe administration of naloxone in the period after operation was achieved in both groups with bolus injections and a continuous infusion.

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JET VENTILATION USING LOW OR HIGH FREQUENCIES, DURING BRONCHOSCOPY

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SUMMARY

Jet ventilation, through a bronchoscope, was evaluated using a lung model (normal compliance and increased airway resistance). Three I/E ratios (0.25, 0.43, 0.67) and seven rates of ventilation (from 20 to 230 cycles per min (c min^{-1})) were studied with the bronchoscope either unoccluded or partially occluded by a telescope. Increases in I/E ratio induced increases in minute ventilation, peak airway pressure, end-expiratory pressure and lung volume. Increase in the rate of ventilation decreased peak airway pressure, increased end-expiratory pressure and lung volume; minute ventilation increased in parallel with the increase in the rate of ventilation or remained constant when a high I/E ratio was used. The introduction of the telescope reduced minute ventilation, as a result of a decrease in the amount of air entrained, and increased end-expiratory pressure and lung volume. The risk of barotrauma as a result of high peak pressure is reduced during high frequency jet ventilation, but the increase in lung volume, particularly when the telescope is introduced, may be of clinical importance.

Jet ventilation, used commonly during bronchoscopic examination (Sanders, 1967; Cromwell, Hirshman and McCullough, 1975; Eriksson and Sjöstrand, 1977; Borg, Eriksson and Sjöstrand, 1980) and, more recently, during the management of tracheobronchial stenosis using a laser beam (Toty et al., 1981; Vourc'h et al., 1983a), can be provided through a rigid or a fibreoptic bronchoscope (Satyanarayana et al., 1980). High frequency jet ventilation is popular because the increase in airway pressure is minimal (Sjöstrand, 1980), while alveolar gas exchange remains adequate in many patients (Carlon et al., 1981; Schuster et al., 1981; Rouby et al., 1983), even in those with severe airway stenosis (Vourc'h et al., 1983a, b). Moreover, the low airway pressures may decrease the risk of barotrauma, a complication of jet ventilation using the Sander's method. However, assessment of high frequency jet ventilation in this setting is difficult since the volume of ventilation cannot be measured using commonly available devices. Furthermore, obligatory air entrainment during all methods using jet ventilation, except those using the pneumatic valve principle (Borg, Eriksson and Sjöstrand, 1980), can be modified during bronchoscopy by the introduction via the bronchoscope of instruments which decrease its lumen and alter the volume of ventilation and airway pressure.

In the present study, we have simulated jet ventilation (low or high frequency), using a standard available jet ventilator during bronchoscopy, and noted the alterations in peak "airway" pressure, end-expiratory pressure and "lung" volume.

MATERIALS AND METHODS

The apparatus is shown in figures 1 and 2.

A rigid Storz bronchoscope (internal diameter 10 mm) was modified by welding a 2.5-mm brass tube on the outer side, the opening of the tube lying obliquely 8 cm from the tip of the bronchoscope. An IDC jet ventilator model VS 600 (Acutronic, Medical System AG, Switzerland) was connected to the tube through a 100-cm low compliance catheter.

The bronchoscope was connected to a bialveolar "lung model" (approved as a reference by the International Meeting of the ISO Commission, June 1983, Stockholm) with a deadspace of 77.5 ml, a

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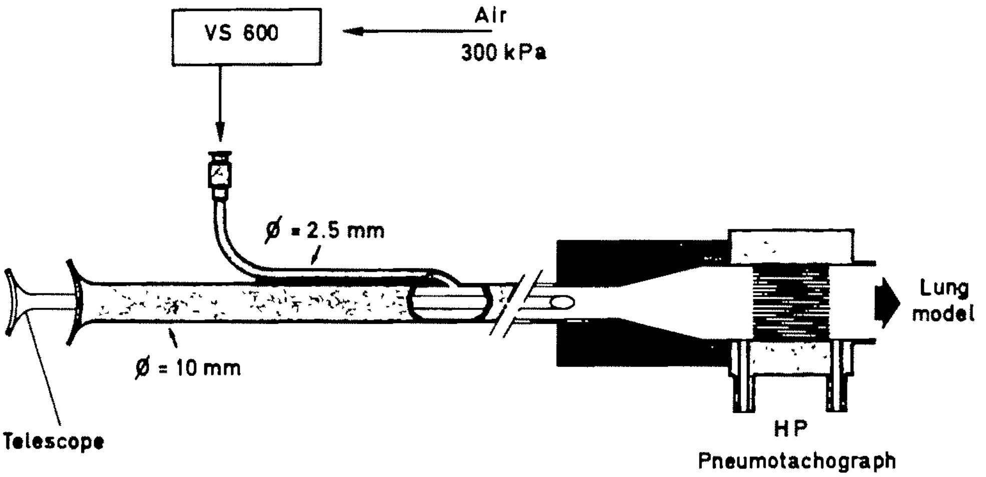

FIG 1. The bronchoscope and the injector. (Angle of opening:60°.)

normal static compliance of 1.41 litre kPa^{-1} (138 ml cm H_2O^{-1}) and a functional residual capacity of 3.24 litre (helium dilution). The bronchial resistance was achieved by a 6-mm diameter orifice; this represented a parabolic resistance of 1.57 kPa/(litre $s^{-1})^2$ (16.02 cm H_2O/(litre $s^{-1})^2$), which is higher than a normal total airway resistance (linear resistance of 0.25 kPa/(litre s^{-1})).

Flow was measured with a Fleisch No. 1 pneumotachograph (Hewlett–Packard) which can measure flow rates up to 2.6 litre s^{-1}, its linearity, from 0 to 75% of maximum flow, being 1.25%. Thus the flow could be measured accurately, since the maximum flow observed was 1.5 litre s^{-1}.

Tidal volumes were obtained by integrating the flow signal (Hewlett–Packard integrator 8816 A). Minute ventilation (litre min^{-1}) was calculated as the product of tidal volume and frequency of ventilation.

Airway pressure was measured (Hewlett–Packard

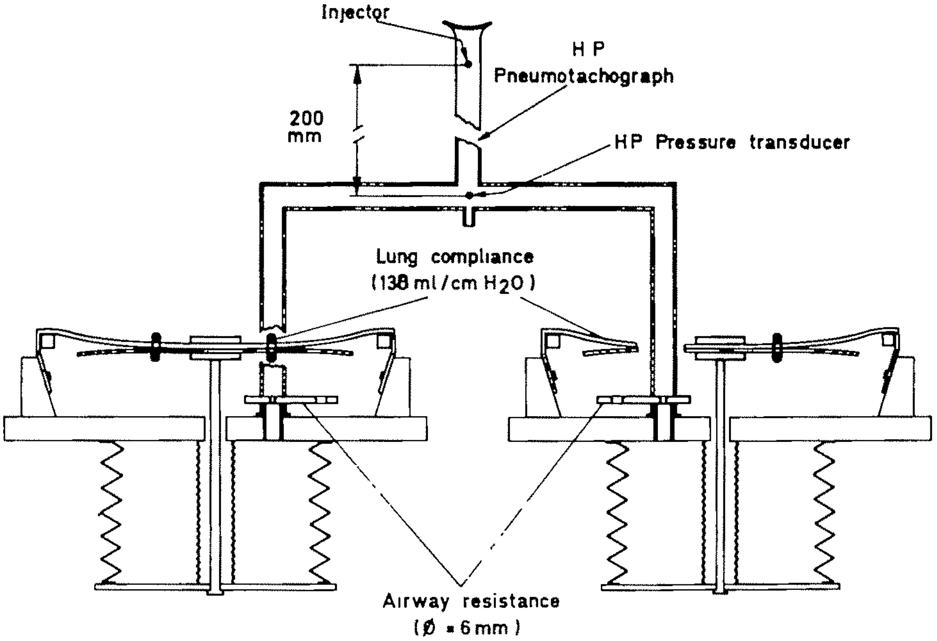

FIG 2. The lung model.

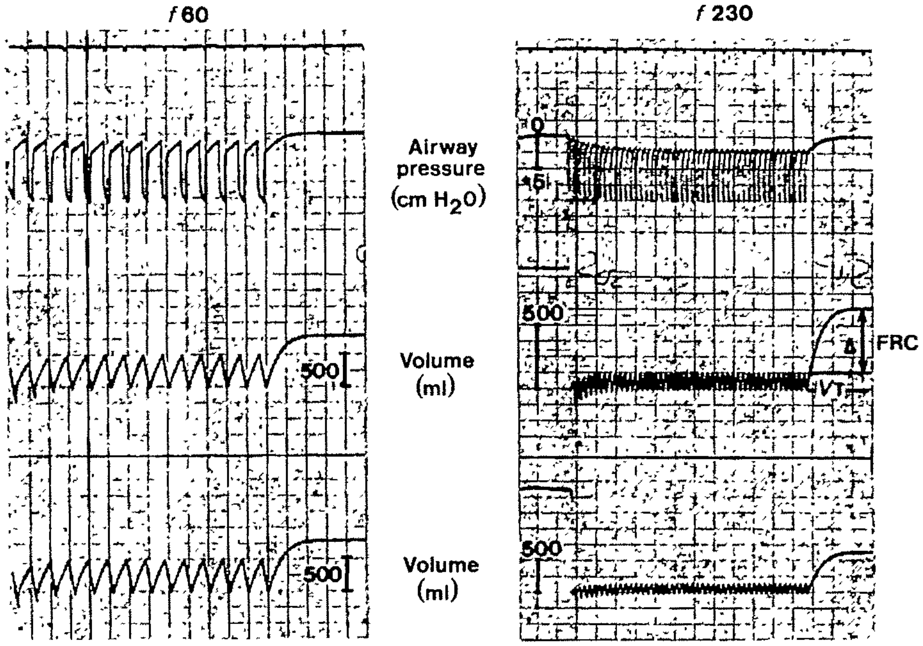

FIG 3. Example of the tracing at two different rates of ventilation. Top trace: airway pressure; middle and bottom traces: volume of ventilation. Inspiratory volumes were bigger than expiratory during the initial period of ventilation; this induced an increase in end-expiratory and peak pressures. Following a period of stabilization, the ventilator was turned off and the increase in functional residual capacity could be measured.

pressure transducer No. 270) laterally at the carina of the model. Peak inspiratory and end-expiratory pressures were expressed as (cm H_2O).

Increase in functional residual capacity, above the resting volume, was assessed at the end of each period of ventilation when the lung model emptied.

All signals were amplified (HP 8802 A and 8805 C amplifiers) and recorded on a HP 7754 B four-channel recorder.

The responses in frequency of the pneumotachograph and of the pressure transducer were studied with a sinewave pressure generator (Institut National de la Santé et de la Recherche Médicale U14, Nancy, France) and found to have a flat response up to 5 Hz for the pneumotachograph and up to 20 Hz for the pressure transducer.

Ventilation was with air and a driving pressure of 300 kPa, the I/E ratio being 0.25, 0.43 or 0.67. The rates of ventilation studied were 20, 40, 60, 90, 110, 170 and 230 cycles per min (c min^{-1}).

All measurements were made (i) with jet ventilation of the lung model through an empty bronchoscope and (ii) with jet ventilation of the lung model following the introduction through the bronchoscope of a telescope which produced a 30% reduction in its lumen.

RESULTS

Measured rates of ventilation differed from those displayed on the ventilator, but they were stable irrespective of any other modifications to the ventilator settings. An example of the tracing obtained is shown in figure 3.

Minute ventilations during ventilation of the lung model with and without the telescope inserted are shown in figure 4. Minute ventilation increased in parallel with the increase in rate of ventilation when the I/E ratio was 0.25 (19 litre min^{-1} at a rate of 20 c min^{-1}, 23 litre min^{-1} at a rate of 230 c min^{-1}); when I/E was 0.43, minute ventilation increased in parallel with the increase in the frequency of ventilation up to 90 c min^{-1} (28.7 litre min^{-1} at a rate of 20 c min^{-1}; 31.5 litre min^{-1} at a rate of 90 c min^{-1}) and then remained stable; when I/E was 0.67, minute ventilation increased up to 60 c min^{-1} (34.9 litre min^{-1} at a rate of 20 c min^{-1}; 36 litre min^{-1} at a rate of 60 c min^{-1}). The increase in I/E ratio induced an increase in minute ventilation; for example when the rate of ventilation was 110 c min^{-1} minute ventilation was 22, 31.5 and 36 litre min^{-1} for the three increasing ratios, respectively.

Introduction of the telescope induced a decrease

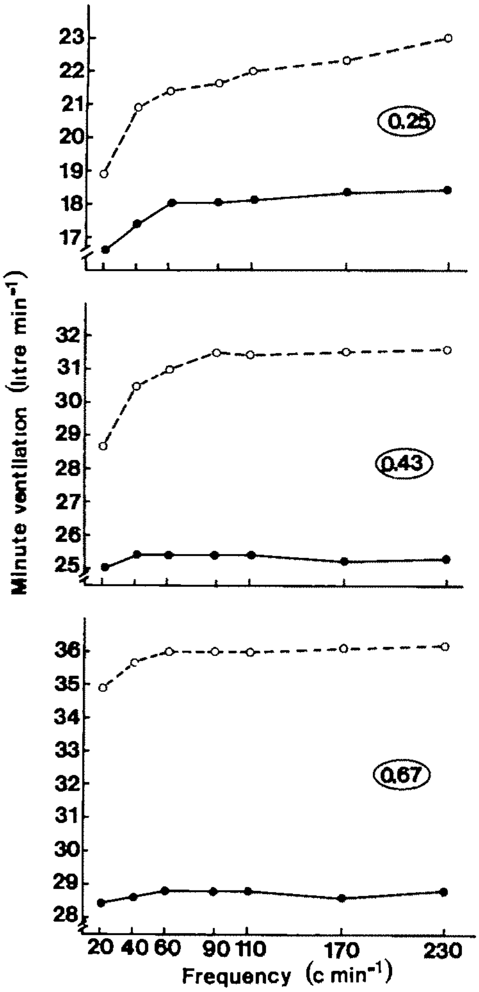

FIG. 4. Variation of minute ventilation when the rate of ventilation was increased, studied at three I/E ratios (0.25, 0.43, 0.67). --- = Bronchoscope alone; —— = telescope inserted.

in minute ventilation. For example, at a rate of 110 c min^{-1}, the decreases in ventilation associated with the three increasing I/E ratios, when a telescope was inserted, were 18, 19 and 20% of the values observed when the bronchoscope was not obstructed. Minute ventilation varied less when the rate of ventilation was increased. Peak airway pressure (fig. 5) decreased in parallel with the increase in the rate of ventilation when the I/E ratio was 0.25 (11.1 cm H_2O at a rate of 20 c min^{-1}; 8.1 cm H_2O at a rate of 230 c min^{-1}); when I/E was 0.43, peak airway pressure decreased in parallel with the increase in the rate of ventilation up to 90 c min^{-1}; 12.6 cm H_2O at a rate of 20 c min^{-1}; 10.6 cm H_2O at a rate of 90 c min^{-1}) and then remained stable; when I/E was 0.67, peak airway pressure decreased up to 90 c min^{-1} (13.9 cm H_2O at 20 c min^{-1}; 11.6 cm H_2O at 90 c min^{-1}). End-expiratory pressures (fig. 5) increased with the rate of ventilation. The increases in I/E ratio induced a parallel increase in both pressures. For example, when the rate of ventilation was 230 c min^{-1}, the end-expiratory pressure was 0.9, 2.3, 3.5 cm H_2O for the three increasing I/E ratios. Introduction of the telescope produced a decrease in peak airway pressure and an increase in end-expiratory pressure.

Increases in functional residual capacity above resting values are shown in figure 6. Functional residual capacity increased with both the increase of the I/E ratio and the increase in the rate of ventilation. When the rate of ventilation was 110 c min^{-1}, the increases in functional residual capacity were 130, 400 and 760 ml for the three increasing I/E ratios. Introduction of the telescope produced an 18% increase in functional residual capacity. The increases in functional residual capacity and end-expiratory pressure were closely related (fig. 7).

DISCUSSION

During bronchoscopic examination and laser surgery for tracheal stenosis, high frequency jet ventilation provides adequate ventilation up to a rate of 300 c min^{-1} with a driving pressure of the injected gases of 500 kPa and an I/E ratio of 0.25 (Vourc'h et al., 1983a, b). This method has certain advantages, particularly during laser surgery when a still surgical field is sought (Vourc'h et al., 1983a). However, changes resulting from the introduction of devices to the bronchoscope and consequent modification in the air entrainment are difficult to evaluate in clinical use. In the present study, we measured tidal volume, airway pressure and functional residual capacity during low- and high-frequency jet ventilation, and the changes produced by the introduction of the telescope. The only limitation was the rate of ventilation, because the pneumotachograph was no longer linear at rates greater than 300 c min^{-1}. In clinical practice this rate of ventilation appears to be the highest which can be used during bronchoscopy in patients with severe airway stenosis (Vourc'h et al., 1983b) or in patients with respiratory failure after operation (Rouby et al., 1983).

Jet ventilation of the lung model

The jet ventilator VS 600 works like a flow interruptor and, therefore, provides constant minute ventilation whatever the rate of ventilation. The increase in minute ventilation parallel with the

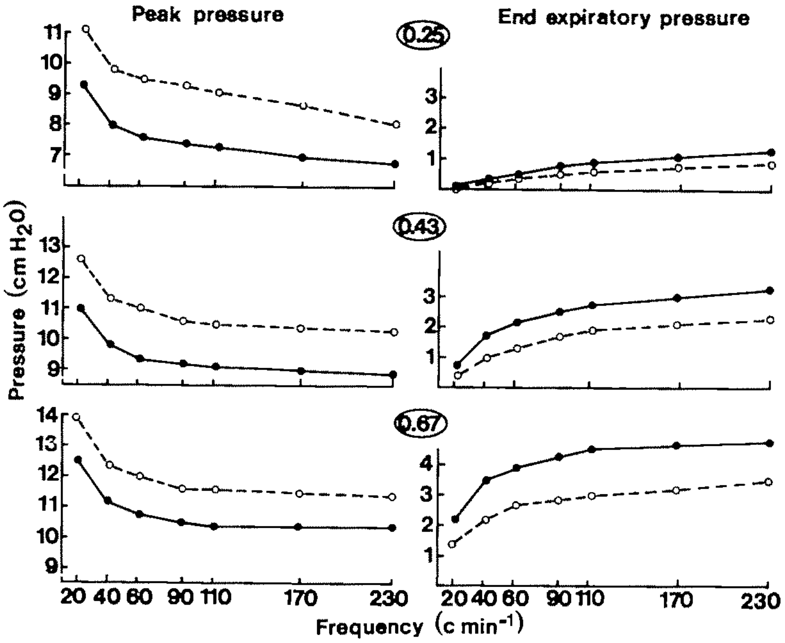

FIG 5. Variation of airway pressure when the rate of ventilation was increased, studied at three I/E ratios (0.25, 0.43, 0.67). — = Bronchoscope alone; —— = telescope inserted.

increase in rate of ventilation (observed when the I/E ratio was 0.25 or 0.43) can be accounted for by a modification of air entrainment; air entrainment depended upon airway pressure facing the injector during the injection phase—that is, peak pressure. We have observed that minute ventilation increased as peak airway pressure decreased, and remained constant when peak pressure was stable—the lower the peak airway pressure, the more important the amount of air entrained*. This was true when the I/E ratio was relatively low (0.25 or 0.43); with an I/E ratio of 0.67, the amount of air entrained was constant, probably as a result of the increase in end-expiratory pressure, maintaining high peak pressures.

The increase in functional residual capacity above the resting value was related to the rate of ventilation and to the I/E ratio. An increase in functional residual capacity has been described using high frequency positive pressure ventilation (Eriksson and Sjöstrand, 1980; Jonzon, Rondio and Sedin, 1980), and during high frequency jet ventilation (Rouby et al., 1983). In the latter study, the increase in functional residual capacity did not follow the increase in rate of ventilation and this was probably the result of the lower static respiratory compliance of the patients studied.

The increase in functional residual capacity has been related to the increase in mean airway pressure (Rouby et al., 1983); in our study it appeared to be related closely to values of end-expiratory pressure and, therefore, a real PEEP effect can be advocated even during high rates of ventilation.

Clinical implications

Using a driving pressure of injected gases of 300 kPa and irrespective of the I/E ratio or rate of ventilation (up to 230 c min^{-1}), the tidal volume is probably greater than the normal anatomical deadspace, itself reduced by the distal position of the injector. This explains in part the efficiency of high frequency jet ventilation. Furthermore, our bronchoscope was designed with an oblique (60°) flow of injection to reduce peak airway pressure, and this also reduces air entrainment.

Our results show an increase in minute ventilation following an increase in rate of ventilation. In a previous study using high frequency oscillation, Rossing and colleagues (1981) demonstrated a relationship between carbon dioxide elimination and the

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*Another explanation for the increase in minute ventilation when the I/E ratio was 0.25 could be that there was imperfect closure of the solenoid valve. However, when the proximal part of the bronchoscope was occluded and the distal part was open to air, we have observed a +3% variation in injector flow between 20 and 230 c min^{-1}.

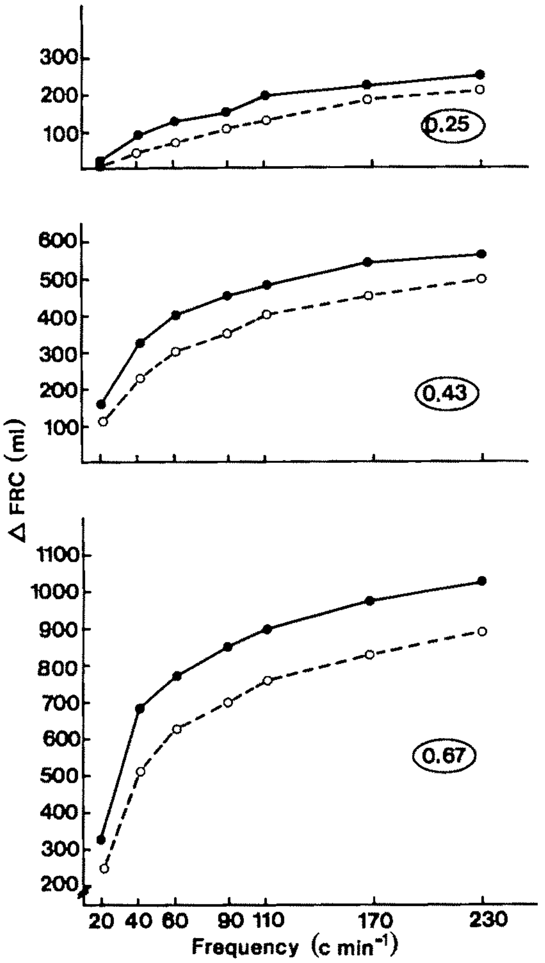

FIG 6. Increase in functional residual capacity (FRC) of the lung model when the rate of ventilation is increased studied at three I/E ratios (0 25, 0.43, 0.67) — = Bronchoscope alone; —— = telescope inserted.

product of respiratory frequency and tidal volume below 200 c min^{-1}, and the tidal volume alone at higher rates of ventilation.

During clinical use in the operating room, it is impossible to obtain the same $F\mathrm{I}_{\mathrm{O}_2}$ in the driving and in the entrained gases (room air). The $F\mathrm{I}_{\mathrm{O}_2}$ of the inspired gas will, therefore, depend upon the respective proportion of the driving gas and the air entrained (Jardine, Harrison and Healey, 1975). It is a reasonable assumption that, when the rate of ventilation is increased and a low I/E ratio used, the $F\mathrm{I}_{\mathrm{O}_2}$ of the inspired gas will decrease, and that when a high I/E ratio is used, it will not change.

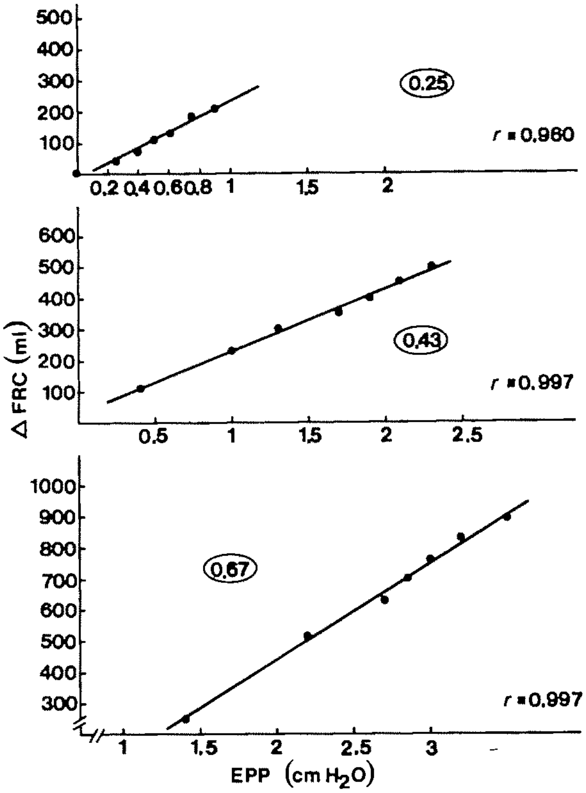

FIG 7. Relationship between end expiratory pressures and increase in functional residual capacity (FRC) of the lung model at three I/E ratios (0.25, 0.43, 0.67).

The decrease in minute ventilation when the telescope was introduced to the bronchoscope reflects a decrease of entrained air; this may have important consequences for carbon dioxide elimination. At the same time, the inspired $F\mathrm{I}_{\mathrm{O}_2}$ will increase, explaining the increase in $P\mathrm{a}_{\mathrm{O}_2}$ reported in this situation (Saarnivaara and Tarkkanen, 1983).

Variation in minute ventilation, following an increase in the rate of ventilation, is less important with the telescope *in situ*. This is possibly because of a high resistance within the bronchoscope, since the amount of air entrained is no longer affected by the airway pressure. Introduction of the telescope induces an increase in lung volume which depends on the rate of ventilation and the I/E ratio; variation of lung volume is particularly important when a high I/E ratio is used.

The benefits of high frequency jet ventilation include a decrease in the risk of barotrauma, but the risk of a major increase in lung volume must be considered. To avoid an excessive increase in lung volume, a low I/E ratio must be used when static respiratory compliance is normal or high (such as in patients with chronic obstructive pulmonary disease). The risk of barotrauma seems to be more important when a telescope is introduced to the bronchoscope.

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EFFECT OF INTRATHECAL DIAMORPHINE ON THE ADRENOCORTICAL, HYPERGLYCAEMIC AND CARDIOVASCULAR RESPONSES TO MAJOR COLONIC SURGERY

C. S. CHILD AND L. KAUFMAN

SUMMARY

The effect of the intrathecal administration of diamorphine on the hyperglycaemic, adrenocortical and cardiovascular responses to major colonic surgery were investigated, and the results compared with those obtained in a similar group of patients receiving low doses of fentanyl. In the group receiving intrathecal diamorphine, the hyperglycaemic response was delayed, and the adrenocortical response decreased significantly both during and following surgery; there were no significant cardiovascular responses to incision, and analgesia was prolonged after operation.

Although the endocrine and metabolic sequelae of surgery are caused predominantly by afferent neurogenic input from the site of injury (Engquist et al., 1977), the role of afferents dependent on opiate receptors is uncertain. Recently, the extradural administration of opioid drugs has been shown to decrease the adrenocortical and hyperglycaemic responses in the period after operation (Christensen et al., 1982; Cowan et al., 1982), although no effect could be demonstrated on the stress response during operation (Christensen et al., 1982; Jorgensen, Andersen and Engquist, 1982). However, there have been no investigations of the alterations in the stress response when opioid drugs have been administered intrathecally—a route which may offer more effective analgesia than the extradural route (Sarubin and Gebert, 1982). In this study, we have studied the effects of intrathecally administered diamorphine on the hyperglycaemic, adrenocortical and cardiovascular responses to major colonic surgery, and have compared the results with those obtained in a similar group of patients receiving low doses of fentanyl i.v.

PATIENTS AND METHODS

Sixteen patients aged between 18 and 65 yr were studied. All were free from metabolic, renal, hepatic and cardiovascular disorders and none had received steroid treatment for at least 1 year. All were undergoing major abdominal surgery and gave their informed consent before taking part in the study. Approval of the hospital ethics committee was obtained.

Patients were premedicated with papaveretum 10 mg and hyoscine 0.2 mg i.m. and all the operations began between 08.00 h and 13.00 h. Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v., and endotracheal intubation was facilitated with suxamethonium 1 mg kg^{-1}. Anaesthesia was maintained with nitrous oxide in oxygen, and tubocurarine 0.5 mg kg^{-1} was given to provide muscle relaxation. Halothane 0.5% was administered to any patient showing signs of increased sympathetic activity after the first 15 min of surgery.

Eight patients (group A) received fentanyl 3–5 μg kg^{-1} i.v., and eight (group B) received diamorphine intrathecally via a 25-gauge spinal needle (L3–4 space). The dose of diamorphine was approximately 0.5 mg per 10 kg of body weight administered in normal saline in a volume of approximately 1 ml per 30 cm of patient height (1 ml per 1 ft).

The lungs were ventilated mechanically with a Manley ventilator to an end-tidal carbon dioxide concentration of 3.4 – 4% (Datascope capnograph). Heart rate was obtained from the electrocardiograph, and mean arterial pressure recorded automatically (Dinamap 845 with printer). Physiological

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TABLE I. *Details of patients (mean ± SEM)*

	Group A	Group B
Number	8	8
Age (yr)	47±3.7	44±6.6
Weight (kg)	65.5±4.3	66.5±4.8
Blood loss (ml)	1033±365	1384±121
Blood replaced (ml)	1000±280	1160±320
Sex ratio	5M: 3F	5M: 3F

saline 6–8 ml kg^{-1} h^{-1} was administered, and blood loss assessed by measurement of the drainage in the suction bottles and the weighing of swabs. Blood was replaced as necessary. Neuromuscular blockade was antagonized with atropine and neostigmine at the end of the operation.

After the operation, fluid was administered i.v. as physiological saline 2 litre 24 h^{-1}, and the respiratory rate was observed closely for 12 h in those patients receiving intrathecal diamorphine. The duration of analgesia was recorded as the time between the end of the operation and the time at which the first dose of an analgesic was required.

Blood samples were drawn through a catheter introduced centrally via a median cubital vein under local analgesia before the induction of anaesthesia. Samples were taken before the induction of anaesthesia (S1), 15 min after induction (S2), 30 min after skin incision (S3), 90 min after skin incision (S4), 15 min after the reversal of neuromuscular blockade (S5), and 6 h (S6) and 24 h after surgery (S7).

Plasma for the measurement of cortisol concentration was obtained by the immediate centrifugation of the samples and stored at −20°C until analysed by radioimmunoassay (Corning Immophase kit). Blood glucose concentration was estimated by a routine glucose oxidase method. The within-assay coefficient of variation for the cortisol estimation was 3.5% around a mean value of 117.5 nmol litre^{-1} and 2.7% around a mean value of 909 nmol litre^{-1}, and the between-assay coefficient of variation was 6.5% around a mean of 117.5 nmol litre^{-1}. The precision of the glucose estimation was approximately 1%. Statistical analysis of within- and between-group variations was performed using Snedecor's analysis of variance, and values of P less than 0.05 were considered significant.

RESULTS

Details of the patients studied are give in table I and details of the operations performed in table II. There were no significant differences between the groups with regard to age, sex, weight, blood loss or operation performed. All the patients in group A required 0.5% halothane and increments of fentanyl during periods of surgical stress such as traction on the mesentery, whilst only two patients in group B required 0.5% halothane during similar periods.

Blood glucose

Blood glucose concentrations increased significantly in group A immediately following skin incision and remained significantly higher than preoperative values for the duration of the study (table III). In group B the blood glucose concentration did not increase significantly until the period after operation, but it then remained greater than baseline for the remainder of the study. Because of the wide variation in individual responses, there were no significant differences between the groups.

Plasma cortisol

In group A the mean plasma cortisol concentration increased significantly throughout the surgical procedure and was still above baseline at 24 h (table III). Plasma cortisol concentration also increased significantly in group B, but the changes were less marked and developed more slowly than in group A. The difference between the groups was significant after 90 min of surgery, and in the period after operation.

TABLE II. *Details of operative procedures*

Group A		Group B	
Procedure	No.	Procedure	No.
Simultaneous combined excision of rectum	1	Simultaneous combined excisions of rectum	3
Rectal excisions	2		
Anterior resections	3	Anterior resections	3
Total colectomy	1	Total colectomy	1
Transverse colectomy	1	Transverse colectomy	1

TABLE III. *Mean (SD) concentrations of blood glucose and plasma cortisol. Significance of difference of means from pre-anaesthetic means (S1) shown by* *$P<0.05$, **$P<0.01$. *Differences between groups at each sample time shown as A* v. *B. For explanation of times of sampling see text*

	Sample						
	S1	S2	S3	S4	S5	S6	S7
Blood glucose (mmol $litre^{-1}$)							
Group A	4.0±0.5	3.9±0.5	6.4±2.2*	6.6±1.1**	7.1±1.3**	7.1±1.5**	6.0±0.9**
Group B	4.2±0.5	4.5±0.4	5.0±1.4	5.5±1.6	6.7±1.4*	5.7±1.2*	5.5±1.1*
A *v*. B	ns	ns	ns	ns	ns	ns	ns
Plasma cortisol (nmol $litre^{-1}$)							
Group A	361±131	333±138	794±222**	1023±196**	1224±307**	1481±313**	654±263*
Group B	295±105	224±85	534±189*	731±214**	926±213**	959±225**	692±197**
A *v*. B	ns	ns	ns	$P<0.05$	$P<0.05$	$P<0.005$	ns

Cardiovascular responses

In the period before skin incision, the mean heart rate was significantly slower in group A than in group B. During the 15 min following skin incision, mean heart rate increased significantly in group A but remained unchanged in group B. Mean arterial pressure increased significantly in group A following skin incision, but did not increase significantly in the group receiving intrathecal diamorphine. There were, however, no significant differences between the groups.

Analgesia

The first dose of analgesia after operation was required after 0.97 ± 0.2 h in group A, and after 17.27 ± 3.4 h in group B.

DISCUSSION

Surgery performed under light general anaesthesia leads to the release of cortisol (Clarke, Johnston and Sheridan, 1970) and to hyperglycaemia (Clarke, 1970). These responses may be abolished at a spinal level by blockade of all afferent and efferent nerve pathways with local analgesia (Engquist et al., 1977). The use of high doses of opioid drugs i.v. may eliminate the adrenocortical and hyperglycaemic responses to pelvic surgery (Hall et al., 1978) and can decrease the responses during gastric surgery (Cooper et al., 1981), but it is thought that this inhibition is brought about at a pituitary or hypothalamic level. Low doses of opioid drugs administered into the extradural space will decrease the stress response, but only during the period after

TABLE IV. *Mean (±SD) values of mean arterial pressure and heart rate following skin incision.* **Significant increase from time 0* ($P<0.05$). *Difference between groups shown by A* v. *B*

	Time after skin incision (min)					
	0	3	6	9	12	15
Mean arterial pressure (mm Hg)						
Group A	71±12	77±12	86±15	96±20*	90±18	93±14*
Group B	75±10	81±11	83±14	92±24	85±14	85±14
A *v*. B	ns	ns	ns	ns	ns	ns
Heart rate (beat min^{-1})						
Group A	54±8	56±6	62±8	71±8*	74±9*	77±10*
Group B	71±15	65±11	65±9	70±13	70±13	71±12
A *v*. B	$P<0.05$	ns	ns	ns	ns	ns

operation (Christensen et al., 1982; Cowan et al., 1982). The results of this study suggest that high doses of intrathecal diamorphine will suppress the stress response both during and after operation.

The effect of spinally administered opioid agents on the stress responses may be dose-dependent, as has been suggested previously (Bromage, Camporesi and Chestnut, 1980). This may explain the failure of extradural morphine 4 mg to produce any reduction in the stress response during surgery in previous studies (Christensen et al., 1982; Jorgensen, Andersen and Engquist, 1982). The relief of pain after operation requires between 5 mg and 10 mg of extradural morphine (Bromage, Camporesi and Chestnut, 1980; Weddel and Ritter, 1981) and, obviously, the nociceptive stimuli during operation will be considerably greater. In addition, morphine, being poorly lipid soluble, is slow to cross the dura (Tung and Yaksh, 1982) and the onset of analgesia may be delayed for up to 1 h after administration (Weddel and Ritter, 1981). The administration of relatively large doses of opioid drugs into the subarachnoid space allows rapid and maximum contact between drug and receptor site. However, nociceptive information is also carried by afferents dependent on gamma-amino-butyric-acid which are unaffected by opiates (Niv, Whitwam and Loh, 1983), by sympathetic and proprioceptive afferents, which are also unaffected by opiates (Calvillo, Henry and Neuman, 1974; Kitahata and Collins, 1982) and possibly by vagal afferents (Bromage, Shibata and Willoughby, 1971), which will be unaffected by spinal afferent blockade. All these pathways may play a part in the initiation of the stress response. Opiates are more potent against C fibre input than against $A\delta$ fibre input, that is, against "slow" pain rather than "fast" pain (Yaksh, 1978). This may explain why there was only a small decrease in the stress responses during operation, when both $A\delta$ and C fibres were being stimulated, and a more marked inhibition of the adrenocortical response in the period after operation, when "slow" pain is predominant.

The differences in heart rate between the groups *before* the onset of surgery were the result of the vagal effect of fentanyl. However, in the fentanyl group there was a significant increase in heart rate and arterial pressure when surgery began, whereas this was not the case in the intrathecal diamorphine group. The cardiovascular stability and prolonged postoperative analgesia afforded by the use of intrathecal diamorphine are obvious advantages. However, the spinal administration of opioid agents has been associated with complications, most notably delayed respiratory depression (Glynn et al., 1979; Scott and McLure, 1979; Davies, Toolhurst-Cleaver and James, 1980), probably as a result of cephalad spread of the opioid, either in the cerebrospinal fluid (Bromage, 1981) or via venous plexuses (Tung and Yaksh, 1982). The fact that this complication occurs rarely and the observation that there is lack of significant spread of ^{3}H-morphine beyond a few centimetres from the subarachnoid injection site (Kitahata and Collins, 1981) suggest that special conditions must exist to cause cephalad spread; for instance, an increased intra-abdominal pressure causing a reversal of flow in the peridural venous plexuses, or an alteration in position causing a change in the flow of cerebrospinal fluid (McCaughey and Graham, 1982). The use of diamorphine rather than morphine may lessen the risk of respiratory depression because its higher lipid solubility will allow it to be taken up more rapidly into the lipid layers of the spinal cord. On the other hand, diamorphine is hydrolysed to morphine and mono-acetylmorphine which, being water soluble, may remain for some time in the cerebrospinal fluid (Way, Young and Kemp, 1965). Blood-gas tensions were not measured in this series of patients, and records of respiratory rate are not complete. However, although the respiratory rate decreased to 10 b.p.m. in two patients, no patient required treatment for respiratory depression.

In conclusion, we have demonstrated that the intra-operative intrathecal administration of diamorphine can produce cardiovascular stability, prolonged postoperative analgesia and a decrease in the stress response during and after operation. Its use deserves further investigation.

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EFFECTS OF THE EXTRADURAL ADMINISTRATION OF MORPHINE OR BUPIVACAINE, ON THE METABOLIC RESPONSE TO UPPER ABDOMINAL SURGERY

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SUMMARY

The influence of thoracic extradural local anaesthetics (0.5% bupivacaine) or extradural morphine on the metabolic response to upper abdominal surgery was compared with the administration of morphine i.v. in the period after operation. The extradural local anaesthetic group had significantly lower blood glucose and plasma FFA concentrations and consistently, but not significantly, lower blood glycerol and lactate concentrations than both the other groups. At 4 h both extradural groups had significantly lower plasma FFA and blood 3-hydroxybutyrate concentrations than the control group. Blood alanine concentration decreased in all three groups with a minimum at 24 h. There were no differences in serum insulin concentrations between the groups. It is concluded that thoracic extradural morphine differs from thoracic extradural local anaesthetics in being much less able to suppress the metabolic response associated with upper abdominal surgery.

Moderate surgical trauma such as cholecystectomy or hysterectomy results in significant endocrine and metabolic responses (Stjernström, Jorfeldt and Wiklund, 1981; Christensen et al., 1982; Jørgensen, Andersen and Engqvist, 1982; Traynor et al., 1982). However, although extradural blockade with local anaesthetics can suppress most of the response associated with lower abdominal surgery (for review, see Kehlet, 1982), less is known as to the effects of extradural blockade on the stress response associated with upper abdominal surgery (Bromage, Shibata and Willoughby, 1971; Traynor et al., 1982; Asoh et al., 1983).

In a previous paper we discussed the *endocrine* effects of extradural local anaesthetics and extradural morphine after upper abdominal surgery (Rutberg et al., 1984a). The main finding was that extradural local anaesthetics almost completely abolished the catecholamine response, whereas extradural morphine did not suppress the increase in plasma adrenaline concentration and suppressed only partly the increase in plasma noradrenaline concentrations. Although the extradural administration of local anaesthetics or morphine did not suppress the cortisol release immediately after surgery, subsequent postoperative values were lower in both of these groups when compared with a control group. Furthermore, the pain relief in both extradural groups was significantly better than in the control group (morphine i.v.).

The metabolic implications of suppression of the hormonal response by extradural morphine remain unclear. There are disparate results concerning postoperative concentrations of glucose, the only metabolite studied previously in connection with extradural morphine (Christensen et al., 1982; Cowen et al., 1982; Jørgensen, Andersen and Engqvist, 1982).

The present study was undertaken to evaluate the *metabolic* consequences of suppression of the endocrine response by extradural morphine and extradural local anaesthetics.

PATIENTS AND METHODS

The study included 24 otherwise healthy women undergoing elective cholecystectomy. The details of the patients have been described previously (Rutberg et al., 1984a). The investigation was approved

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by the local Ethics Committee and informed consent was obtained from each patient. They were randomly allocated to one of the groups: C (control), L (local anaesthetic) and M (morphine). The groups were comparable with regard to age (43.0 ± 4.2, 45.5 ± 4.1, 40.1 ± 3.4 yr (mean + SEM), weight 73.6 ± 4.5, 66.4 ± 4.8, 75.0 ± 3.8 kg), duration of surgery (70 ± 6, 73 ± 10, 72 ± 3 min) and estimated blood loss (234 ± 50, 228 ± 52, 233 ± 53 ml), respectively.

The patients were in a postabsorptive state after an overnight fast and were premedicated with diazepam 10–15 mg rectally 1.5–2 h before surgery. All operations started between 08.30–09.30 a.m. and the patients remained in the postoperative ward for 24 h. Before the induction of anaesthesia, physiological saline 500 ml was given i.v. This infusion was continued during surgery at a rate of 6 ml kg^{-1} h^{-1}, and in the period after operation at a rate of 1–2 ml kg^{-1} h^{-1}. Blood loss was replaced with Dextran 70. No other i.v. infusions were given during the investigation.

One hour before surgery an extradural catheter was placed (T9–10 or T10–11 spaces) in groups L and M. In group L, 0.5% bupivacaine 7 ml was given to produce a segmental blockade from T4 to L3 as evaluated by pin-prick. Throughout the study this level of blockade was maintained by repeated doses of 0.25% or 0.375% bupivacaine 5–8 ml. In group M, morphine 4 mg dissolved in isotonic saline 7 ml was given extradurally. Repeated doses of morphine 4 mg were then given every 10 h. After the study the correct position of the catheter in group M was confirmed by a small dose of local anaesthetic.

In all groups general anaesthesia was induced with thiopentone and fentanyl. Endotracheal intubation was facilitated with pancuronium, and anaesthesia maintained with nitrous oxide in oxygen (3:1.5 litre min^{-1}) using a circle system with soda-lime absorption. Repeated doses of fentanyl, pancuronium and diazepam were given. The doses of fentanyl (mean ± SEM) were 0.55 ± 0.05, 0.35 ± 0.03, 0.50 ± 0.04 mg in groups C, L and M, respectively. The dose in group L was significantly ($P < 0.05$) smaller than in groups C and M. The control group received morphine 2–5 mg i.v. as required to provide analgesia after operation.

Arterial blood samples for analysis of hormones and energy metabolites were taken 1 h before surgery and 2, 4, 6, 12 and 24 h after skin incision. Serum insulin concentrations were determined by the Phadeseph Insulin RIA (Pharmacia), based on solid phase double-antibody precipitation. All blood samples for assay of metabolites were immediately precipitated with ice-cold perchloric acid. After centrifugation, the protein-free extract was deep-frozen (−80 °C) pending analysis. The analyses were performed by microfluorimetry: D-glucose by modification for fluorimetry of the hexokinase method described by Schmidt (1961) and Barthelmai and Czok (1962) and lactate, glycerol, 3-hydroxybutyrate and alanine as described previously (Jorfeldt and Juhlin-Dannfeldt, 1977). Free fatty acids (FFA) were analysed according to Ho (1970). Oxygen consumption was measured 1 h before surgery and at 4, 6, 12 and 24 h after skin incision. The expired air was collected in a Douglas bag and then analysed using a mass spectrometer (the coefficient of variation of a single determination was 3.3%).

Statistical methods and presentation of data

One- and two-way analysis of variance and Duncan's new multiple range test were used (Winer, 1971). The term "significant" implies statistically significant. Tests were made at the 1% and 5% level. Data are presented as mean values ± standard error of the mean (SEM).

RESULTS

Glucose concentration (fig. 1)

The arterial concentration of glucose increased in all groups during surgery ($P < 0.01$). This increase was about 50% in groups C and M, but only 14% in group L. In group C blood glucose concentration remained increased at 2, 4, 6 and 12 h after skin incision ($P < 0.01$). In group M the arterial glucose concentrations were increased at 2, 4 ($P < 0.01$) 6 and 12 h ($P < 0.05$) whereas the only increase in group L was at 2 h. At 24 h the arterial glucose concentration in group L was lower than before the operation ($P < 0.05$). Group L demonstrated lower values than groups M and C at 2 h ($P < 0.05$). Group M and C did not differ.

Insulin concentration (fig. 1)

There were no significant differences in serum insulin concentrations between the three groups, although there was a significant increase in group M at 2 h ($P < 0.01$).

Lactate concentration (fig. 2)

The arterial concentration of lactate showed a pattern of reaction very similar to that of glucose. Thus, the lactate concentration had increased significantly in all three groups 2 h after skin incision (groups C

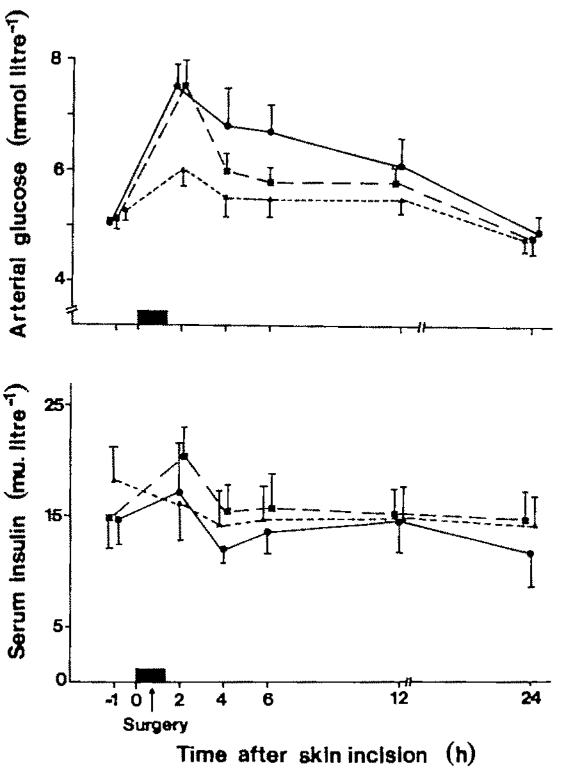

FIG. 1. Blood glucose and serum insulin concentrations (mean ± SEM) before and after cholecystectomy with general anaesthesia (GA) (●——●), GA + extradural local anaesthetics (▲—▲) and GA + extradural morphine (■– –■).

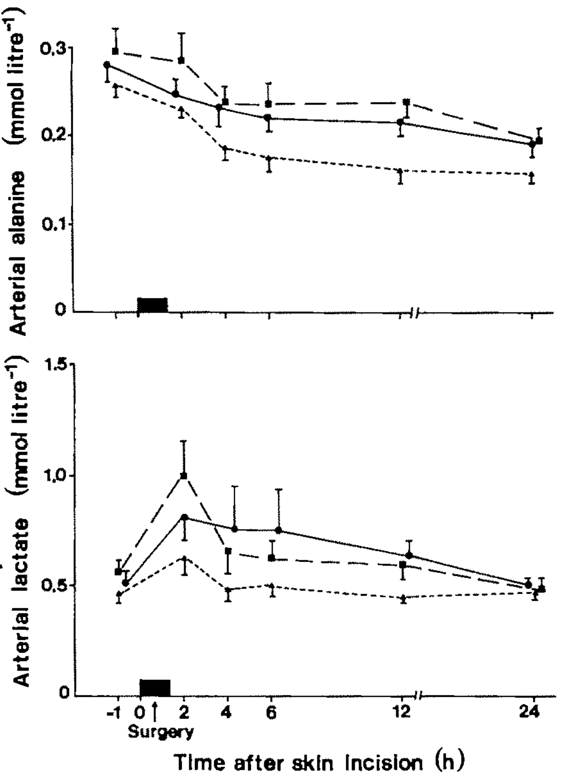

FIG 2. Blood alanine and lactate concentrations (mean ± SEM) before and after cholecystectomy with general anaesthesia (GA) (●——●), GA + extradural local anaesthetics (▲—▲) and GA + extradural morphine (■– –■).

and L $P < 0.05$; group M $P < 0.01$). Thereafter, concentrations decreased and became similar to the values observed before operation. The arterial lactate concentrations in group L were consistently lower than those in groups M and C, but no significant differences occurred.

Alanine concentration (fig. 2)

The arterial concentration of alanine decreased in all groups to about 70% of its value before operation. The decrease was significant by 2 h in groups C and L ($P < 0.05$) and for the remaining period in all groups ($P < 0.01$). No statistical differences were observed between the three groups.

FFA concentration (fig. 3)

The arterial concentration of FFA increased ($P < 0.01$) in group C at 4 and 6 h after skin incision, and in group M at 4 ($P < 0.05$), 6 ($P < 0.01$) and at 24 h ($P < 0.05$) after skin incision. In group L, a decrease was seen at 2 h ($P < 0.05$). At 2 and 4 h significantly ($P < 0.01$) smaller values were seen in group L than in groups M and group C. At 4 h the value in group M was smaller ($P < 0.05$) than that obtained in group C.

Glycerol concentration (fig. 3)

The arterial concentration of glycerol was increased in all groups, but significant ($P < 0.05$) only at 4 h in group C. No significant differences were seen between the three groups, although consistently smaller values were seen in group L when compared with the other groups.

3-Hydroxybutyrate concentration (fig. 3)

The arterial concentration of 3-hydroxybutyrate increased almost continuously in all groups and reached a value about four to five times the preoperative concentration. The increase was significant ($P < 0.01$) at 4, 6, 12 and 24 h in group C, at 6, 12 and 24 h in group M and at 12 and 24 h in group L. The only difference between groups was seen at 4 h, when groups L and M had smaller ($P < 0.01$) values than group C.

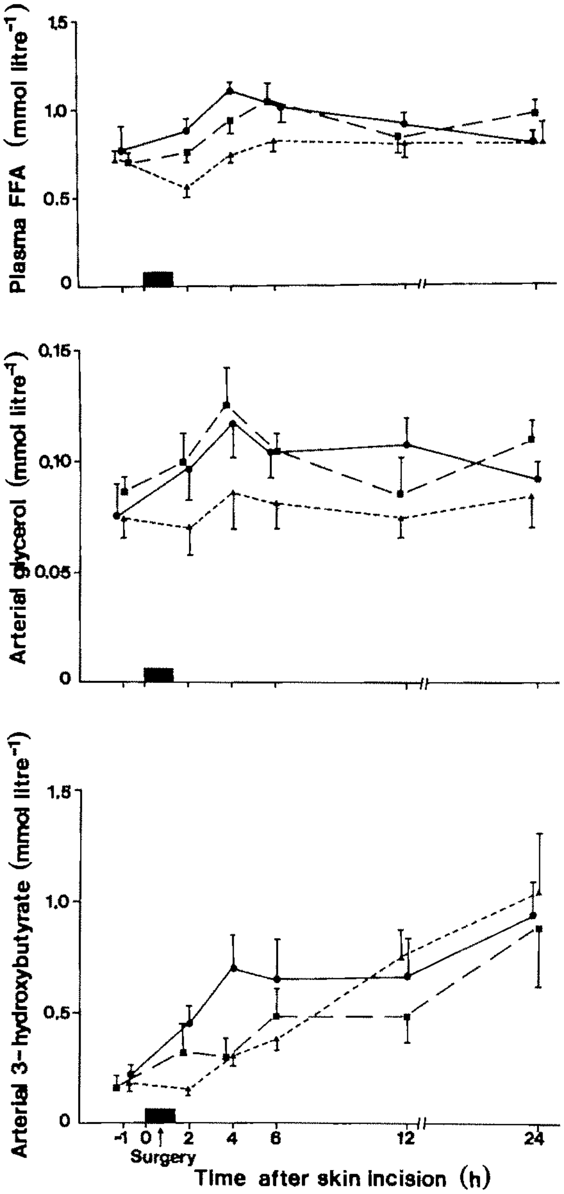

FIG 3. Plasma FFA, blood glycerol and 3-hydroxybutyrate concentrations (mean ± SEM) before and after cholecystectomy with general anaesthesia (GA) (●——●), GA + extradural local anaesthetics (▲ — ▲) and GA + extradural morphine (■– –■)

Oxygen uptake (fig. 4)

Oxygen uptake in group C was increased at 12 and 24 h ($P < 0.01$), and in group L at 6 and 24 h ($P < 0.05$). In group M, as a result of technical problems, only four observations were obtained before the operation. No differences were obtained between the three groups.

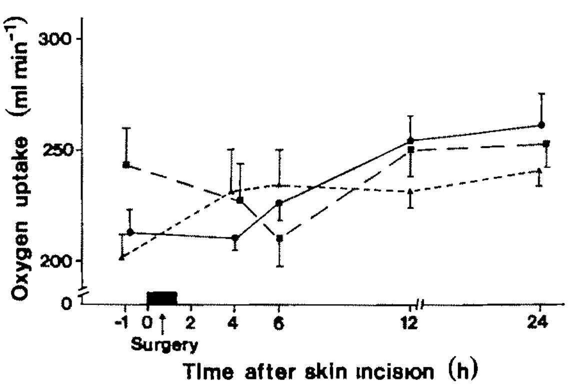

FIG 4. Oxygen uptake (mean ± SEM) before and after cholecystectomy with general anaesthesia (GA) (●——●), GA + extradural local anaesthetics (▲—▲) and GA + extradural morphine (■– –■).

DISCUSSION

The increase in oxygen uptake by about 20% in the present study was slightly higher than that noted by Kinney (1983), but is in accord with the results of other workers after elective surgery (Renck, 1969; Wiklund, 1975; Rutberg et al., 1984b). Pain and relief of pain have been considered to be important factors influencing oxygen uptake in the period after operation (Wiklund, 1975). Although, in the present study, pain relief in both extradural groups was significantly better than in the control group, and the catecholamine concentrations were significantly depressed in the extradural local anaesthetic group, no difference in systemic oxygen uptake was obtained between the three groups. Thus, our results indicate that, in moderate surgical trauma, other factors than pain and catecholamines are involved in the increase in energy expenditure. Such factors could be other hormones or pyrogens.

In the following sections we will discuss first the metabolic response to trauma and the modification of this stress response by local anaesthetics, and then the effects of extradural morphine.

Adrenaline, cortisol and glucagon act synergistically to stimulate hepatic glucose output and counteract the suppressant role of insulin on hepatic glucose production (Gelfand, De Fronzo and Gusberg, 1983). These effects increase the blood glucose concentration and this is often used as a indicator of surgical stress. The magnitude of the hyperglycaemia is proportional to the severity of the trauma (Clarke, 1970; Stoner et al., 1979; Traynor and Hall, 1981) and there is a continuous increase during surgery and immediately afterwards (Stjernström, Jorfeldt and Wiklund, 1981). A maximal increase of 50% in the control group was noted in this study compared with a 14% increase in the extradural local anaesthetic group. This influence on blood glucose concentration by extradural local anaesthetics is of about the same magnitude as that described previously in the early period after operation (Bromage, Shibata and Willoughby, 1971), is slightly greater than that observed in the late peroperative period (Traynor et al., 1982), and is probably the result of adrenocortical and sympathoadrenergic suppression.

In spite of considerably higher blood glucose concentrations following surgery in the control group, the serum insulin concentrations were similar. It is known that trauma decreases the insulin response to hyperglycaemia, probably as a result of α-adrenergic inhibition of β-cell function caused by the release of catecholamines (Halter and Pflug, 1980). Since the blood glucose concentration in the extradural local anaesthetic group was only slightly increased it was not possible, from our data, to evaluate whether the blockade and catecholamine concentrations influenced the insulin–glucose relationship. To clarify this point it would be necessary to study the insulin response to an infusion of glucose (Halter and Pflug, 1980).

Catecholamines, in particular, but also cortisol stimulate lipolysis and oppose the lipogenesis controlled by insulin. Although there are reports that indicate that these catabolic hormones are increased in the plasma after surgery, there is less consensus as to the influence of surgical trauma on fat metabolism (Hall et al., 1978; Kehlet et al., 1979; Stjernström, Jorfeldt and Wiklund, 1981; Traynor et al., 1982; Asoh et al., 1983). This might result from different anaesthetic techniques and surgical procedures, as well as from varying times of sampling in relation to the operation. Although we found marked increase in both plasma FFA and blood glycerol concentrations in the control group, there was no significant change until 4 h after skin incision—that is more than 2 h after the end of surgery. At this time plasma cortisol and plasma catecholamine concentrations were still greater than normal (Rutberg et al., 1984a). It would be expected that there would be a decrease in lipolysis in the extradural local anaesthetic group because of the decrease in sympathoadrenergic stimulation. Certainly, in the present study plasma FFA concentration was significantly lower and blood glycerol concentration consistently but not significantly lower. This accords with the findings of Kehlet and colleagues (1979) and Asoh and co-workers (1983), but is in contrast to those of Traynor and colleagues (1982).

The results of the present study indicate that the suppressant effect of extradural local anaesthetics on the endocrine response after operation is accompanied by metabolic changes. The partial suppression of the *endocrine* response induced by extradural morphine was, however, only to a minor degree reflected by a decrease in the *metabolic* response to the trauma of cholecystectomy. Extradural morphine was unable to suppress significantly the postoperative increase in blood glucose concentration and this accords with the findings of Jørgensen, Andersen and Engqvist (1982). However, it is in contrast to those of Christensen and colleagues (1982), and Cowen and associates (1982), although Cowen and co-workers (1982) used extradural local anaesthetics during surgery and, furthermore, they used extradural diamorphine to provide pain relief after operation. Christensen and colleagues (1982), used morphine 4 mg before operation (as in this study), but at the end of surgery they gave another 4 mg. These differences in procedures might explain the discrepancy between our results and theirs. However, even though a higher dose of extradural morphine may suppress the hyperglycaemic response after surgery, its clinical value is debatable, since the risk of respiratory depression increases with increasing doses of extradural morphine (Rawal and Wattwil, 1984).

The increases in blood or plasma concentrations of glucose, lactate, FFA and glycerol after trauma were suppressed considerably more by extradural local anaesthetics than by extradural morphine. This finding might be explained by the inability of extradural morphine to suppress adrenaline (Rutberg et al., 1984a) which, in this stress situation, is considered to be the prime active metabolic hormone. Furthermore, not only adrenaline but also direct activation of sympathetic nerves to the liver causes hepatic release of glucose (Järhult et al., 1979). These efferent sympathetic nerves to the liver can be blocked by extradural local anaesthetics (Bromage, Shibata and Willoughby, 1971). Extradural opiates, however, are not considered to have any sympathetic blocking effects (Bromage, Camporesi and Leslie, 1980).

Another plausible explanation for the lesser effect of extradural morphine on the metabolic response might be that the metabolic response to trauma, once released, leads to persistent changes, even if afferent stimuli from the injured area are blocked later (Møller et al., 1982). It is well known that it is not possible to achieve surgical anaesthesia with extradural morphine. Therefore, it is possible that the hormonal release initiated by surgery evokes metabolic changes that persist despite the partial postoperative hormonal suppression by extradural morphine.

In conclusion, cholecystectomy induces significant increase in the concentrations of the catecholamines, cortisol, glucose, lactate, FFA, glycerol and 3-hydroxybutyrate. With the exception of 3-hydroxybutyrate, these concentrations increase to a peak in the early period after operation and then decrease rapidly. Extradural local anaesthetics can suppress considerably the catecholamine response and the increases in glucose, lactate, FFA and glycerol concentrations. Although extradural morphine provides pain relief comparable to that of extradural local anaesthetics, morphine is less efficient in decreasing the endocrine response to surgery, and has only a very minor influence on the metabolic response.

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EFFECTS OF THE EXTRADURAL ADMINISTRATION OF LOCAL ANAESTHETIC AGENTS AND MORPHINE ON THE URINARY EXCRETION OF CORTISOL, CATECHOLAMINES AND NITROGEN FOLLOWING ABDOMINAL SURGERY

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SUMMARY

Twenty patients undergoing major abdominal surgery were allocated randomly to receive either general anaesthesia with low-dose fentanyl plus intermittent systemic morphine for postoperative pain or the same general anaesthetic plus extradural analgesia during and following surgery (local anaesthetics from before skin incision until 24 h after skin incision plus extradural morphine 4 mg every 12 h from 3 h to 72 h after skin incision). Postoperative pain scores were lower ($P < 0.05$) in the group receiving extradural analgesia, but this regimen failed to prevent the increase in the urinary excretion of cortisol, adrenaline, noradrenaline and nitrogen both on separate days and on cumulative measurements over 4 days. Pain scores did not correlate to urinary excretion of the various endocrine–metabolic indices either on separate days or over the cumulative 4-day period. It is concluded that the relief of pain **per se** *has no major influence on the catabolic response to abdominal surgery.*

Surgical trauma elicits endocrine and metabolic changes characterized by an increase in the secretion of cortisol and catecholamines, and a net loss of protein. The release mechanisms of this response remain to be defined completely, but pain and other afferent neurogenic stimuli from the site of the operation play a dominant role (Kehlet, Brandt and Rem, 1980). Thus, afferent neurogenic blockade with extradural analgesia using local anaesthetic agents has been demonstrated to inhibit or prevent most of the classical endocrine–metabolic changes following lower (gynaecological) abdominal surgery, and procedures on the lower extremities (Kehlet, 1982). In contrast, extradural analgesia is less efficient in modifying the response associated with major upper abdominal surgery (Bromage, Shibata and Willoughby, 1971; Menzies Gow and Cochrane, 1979; Kossman et al., 1982; Seeling et al., 1982; Traynor et al., 1982; Tsuji, Asoh et al., 1983). Extradural analgesia with morphine alone leads only to a minor suppression of the stress response during the intra-operative and immediate postoperative periods (Christensen et al., 1982; Cowen et al., 1982; Jørgensen, Andersen and Engquist, 1982). However, the relationship between the relief of postoperative pain during extradural analgesia with local anaesthetics and morphine and the stress response has not been evaluated.

The purpose of this investigation was to study the correlations between the relief of pain obtained by an extradural analgesic regimen using local anaesthetics plus morphine, and the urinary excretion of cortisol, catecholamines and nitrogen during the first 4 days after major abdominal surgery in patients on a fixed nutritional intake.

PATIENTS AND METHODS

Twenty patients undergoing elective major abdominal surgery were randomized into two groups. One group (10 patients: seven colonic resections and three gastric resections) had general anaesthesia with low-dose fentanyl (initial dose 0.007 mg kg^{-1}, maintenance dose 0.002 mg kg^{-1} h^{-1}) and nitrous oxide in oxygen. Systemic morphine in doses of 6–10 mg every 4–6 h was given routinely to alleviate

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TABLE I. *Clinical data (mean±SEM) in patients undergoing major abdominal surgery during general or extradural analgesia*

	Sex (M:F)	Age (yr)	Height (cm)	Body weight (kg)	S-albumin (mmol litre^{-1})	S-Transferrin (mmol litre^{-1})	Duration of surgery (min)
General anaesthesia (n=10)	3:7	70±5	161±3	61±4	455±23	31.2±1.7	189±18
Extradural analgesia (n=10)	7:3	65±3	172±3	66±3	447±22	30.9±3.0	156±18
P (between groups)	ns	ns	<0.02	ns	ns	ns	ns

pain after operation. The other group of 10 patients (eight colonic resections, one gastric resection and one cholecystectomy) received the same general anaesthetic technique with, in addition, extradural analgesia (1.5% etidocaine) used during the operation in a dose sufficient to provide sensory analgesia (pin prick) from T4 to S5 before skin incision. The extradural regimen was continued into the period after operation: 3 h after skin incision bupivacaine 10 ml (0.5% without adrenaline) was given and thereafter bupivacaine 5 ml every 4 h for 24 h. In addition, extradural morphine 4 mg was administered every 12 h from 3 to 72 h after skin incision. Thereafter, the patients received systemic morphine 6–10 mg on request.

Clinical data for the two groups are shown in table I.

None of the patients had liver or renal disease as verified by routine laboratory tests, and none showed signs of endocrine disease or was receiving hormone treatment. None of the patients had infective or surgical complications during the 4-day study period.

All patients received 10% dextrose 1000 ml and 1000 ml of an aminoacid–glucose solution (Vaminglucose) i.v. on the day of operation and on each of the following 3 days. This regimen provided 200 g of glucose and 70 g of aminoacids (nitrogen 9.4 g) daily. In addition, sodium chloride and potassium chloride solutions were given i.v. to maintain fluid and electrolyte balance. Oral intake of fluid during the first 4 days after operation was restricted to tap water.

Urine was collected in 24-h periods (the bladder was catheterized in all patients) and the concentrations of creatinine, urea (routine laboratory methods), cortisol (radioimmuno-assay-kit, Amersham), adrenaline, noradrenaline (double-isotope derivative technique) (Christensen et al., 1980) and nitrogen (Kjeldahl-technique) were measured.

Pain was assessed by the patients 24, 48, 72 and 96 h after skin incision, using an arbitrary scale from 0 to 10 (worst pain). Patients were asked to rate the average pain experienced during the preceding 24 h.

The experimental programme was approved by the ethics committee for Copenhagen Hospitals. Informed consent was obtained from all patients.

Student's t test and linear regression analyses were used, and a P-value less than 0.05 considered significant.

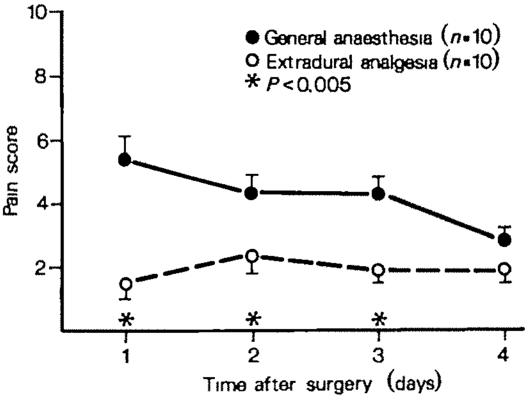

FIG. 1. Pain scores during the first 4 days after major abdominal surgery in patients receiving general anaesthesia and routine systemic morphine intermittently for pain relief, and in patients receiving a combination of general anaesthesia and extradural analgesia during surgery and extradural analgesia with local anaesthetics plus morphine for pain relief after operation.

TABLE II. *Postoperative changes (mean±SEM) in rectal temperature and urinary excretion of creatinine in patients undergoing major abdominal surgery with general or extradural analgesia*

	Before op.	Days after operation			
		1	2	3	4
Rectal temp. (°C)					
General anaesthesia	36.8±0.1	37.7±0.2	37.8±0.1	37.4±0.1	37.1±0.2
Extradural analgesia	37.0±0.1	37.5±0.2	38.0±0.2	37.5±0.2	37.1±0.1
Urinary creatinine excretion (mmol)					
General anaesthesia	—	7.98±0.7	9.68±1.43	8.83±0.95	8.87±1.03
Extradural analgesia	—	11.02±1.4	10.30±0.90	10.75±0.89	10.07±0.96

RESULTS

Postoperative pain scores were significantly lower, during the first 3 days after operation, in the patients receiving the extradural analgesic regimen compared with patients receiving routine management with systemic morphine (fig. 1).

Rectal temperature increased ($P < 0.05$) slightly during the first 3 days after operation, but there was no difference ($P > 0.4$) between the groups (table II).

Urinary excretion of creatinine remained constant throughout the first 4 days after operation in both groups and there were no differences ($P > 0.2$) between the groups (table II). In the individual patients the variability in the creatinine excretion was less than 15% between days, indicating that urinary sampling was sufficient.

The cumulative 4-day postoperative excretion of cortisol (fig. 2) was insignificantly lower (8.2 ± 2.0 μmol) in the extradural group compared with the group receiving anaesthesia plus systemic opiates (10.0 ± 1.5 μmol). The difference in cortisol excretion between the groups was most pro-

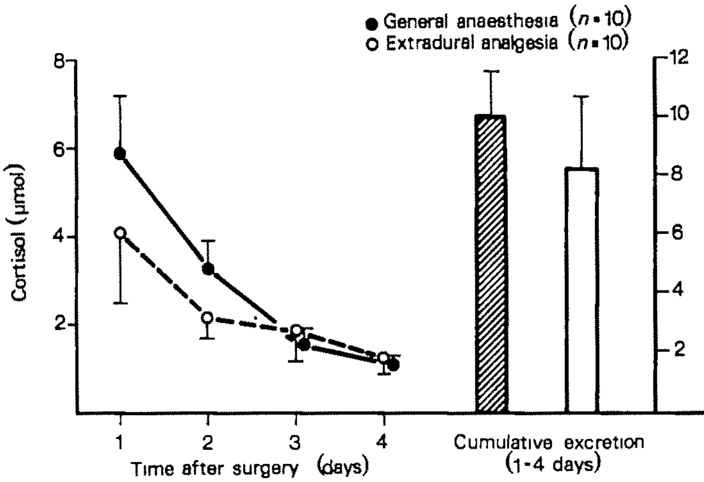

FIG 2. Urinary excretion of cortisol (mean values ± SEM) after major abdominal surgery in patients receiving general anaesthesia plus routine intermittent morphine for pain relief, and in patients receiving general anaesthesia and extradural analgesia during surgery plus extradural analgesia with local anaesthetics and morphine in the period after operation. There were no differences ($P > 0.05$) between the groups in any endocrine–metabolic variable either on separate days or on the cumulative excretion values.

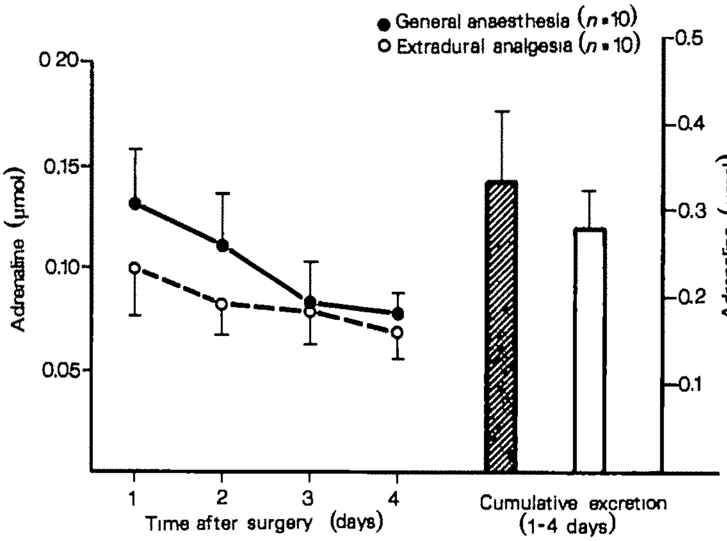

FIG. 3. Urinary excretion of adrenaline after major abdominal surgery. Details as figure 2.

nounced during the first 2 days, but also failed to achieve significance on separate days. On all days cortisol excretion was greatly increased above normal mean values (0.1 µmol/24 h).

Cumulative urinary excretion of noradrenaline (fig. 4) was lower (not significant) in the extradural group (1.3 ± 0.2 µmol) than in the general anaesthesia group (1.9 ±0.2 µmol), and again there were no significant differences between the groups on the separate days. Noradrenaline excretion was increased above normal mean values (0.18 µmol/24 h) on all days in both groups.

Cumulative urinary excretion of adrenaline (fig. 3) was lower (not significant) in the extradural group (0.29 ± 0.05 µmol) compared with the general anaesthetic group (0.34 ±0.07 µmol), and there were no significant differences between the individual days. Adrenaline excretion was increased above normal mean values (0.04 µmol/24 h) every day in both groups.

Urinary excretion of nitrogen (fig. 5) was almost identical in the two groups, both with regard to cumulative values and values on the individual days. The cumulative 4-day nitrogen balance was negative

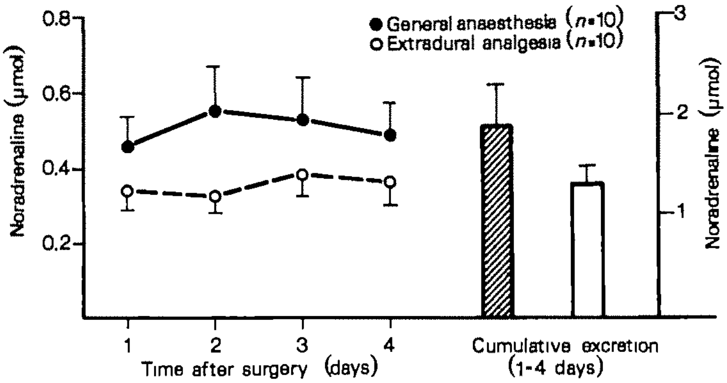

FIG 4. Urinary excretion of noradrenaline after major abdominal surgery. Details as figure 2.

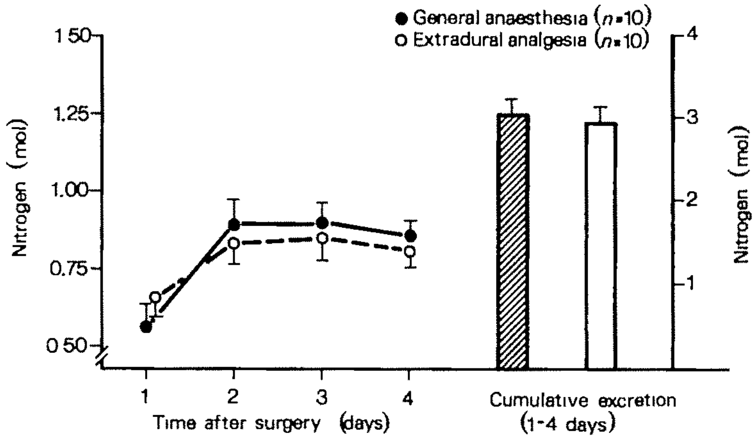

FIG 5 Urinary excretion of nitrogen after major abdominal surgery Details as figure 2.

in both groups (−0.25 ± 0.19 mol in the extradural group and −0.34 ± 0.18 mol in the general anaesthetic group) ($P > 0.7$). The relationship between the cumulative urinary excretion of nitrogen and the urea concentration was linear and similar in the two groups ($r = 0.91, P < 0.001$).

There were no relationships ($P > 0.05$) between the daily pain scores and the urinary excretion of cortisol ($r = 0.18$; 0.01; 0.01; 0.16), adrenaline ($r = 0.05$; 0.13; 0.07; 0.23), noradrenaline ($r = 0.21$; 0.42; 0.25; 0.28) or nitrogen ($r = 0.26$; 0.01; 0.09; 0.02) on days 1, 2, 3 and 4, respectively. Similarly, there were no correlations between the cumulated 4-day pain scores and the urinary excretion of cortisol, adrenaline, noradrenaline and nitrogen ($r = 0.2$; 0.03; 0.35; 0.17, respectively).

DISCUSSION

The results show that an extradural analgesic regimen with local anaesthetics plus morphine provides adequate relief of pain after major abdominal surgery, and is superior to the "routine" management of pain using the intermittent administration of systemic morphine.

Although these findings are in accord with several recent studies, it was surprising that the pain relief achieved did not decrease the catabolic response to surgery, as assessed by the 4-day postoperative urinary excretion of cortisol, catecholamines and nitrogen. Previous investigations have demonstrated that extradural analgesia with local anaesthetics prevented a predominant part of the endocrine–metabolic response to lower (gynaecological) abdominal surgery and procedures on the lower extremities and, concomitantly, these patients were pain free (Kehlet, 1982). However, the existence of a disparity between the relief of pain after operation and modification of the stress response has been suggested in studies where the hyperglycaemic and adrenocortical responses to abdominal hysterectomy were only prevented if sensory analgesia extended to T4 despite adequacy of pain relief in patients with a sensory block to T8 and T10 (Engquist et al., 1977). Similarly, in studies using extradural morphine alone to relieve pain following hysterectomy (Christensen et al., 1982; Cowen et al., 1982; Jørgensen, Andersen and Engquist, 1982), the adrenocortical and hyperglycaemic responses to surgery were only suppressed partially, despite adequate pain relief, indicating that neurogenic pathways other than opiate-receptor dependent nociceptive pathways may be important in mediating the trauma response.

It might be argued that our method of pain assessment consisted of an overall estimation performed retrospectively each day, thereby increasing the risk of overlooking periods with more or less pain. However, the validity of the overall, retrospective assessment has been shown in studies with concomitant, repeated pain score assessments during the study (Rigamonti et al., 1983).

In the present study we used a combination of a local anaesthetic agent and morphine extradurally to obtain more complete afferent blockade. It may be argued that a more pronounced metabolic effect of the extradural regimen could have been overlooked since the randomization between groups was less than ideal in that the patients in the extradural group tended to be slightly younger, taller, heavier and most were male. Such patients have been considered to show a more pronounced catabolic response to trauma, although data on this point are not available. Nevertheless, the excretion of cortisol and catecholamines was increased markedly above upper normal limits in both groups and a major modifying effect of the extradural regimen on the stress response is unlikely, despite the slight skewness in the composition of patients.

Previous investigations have also been unsuccessful in preventing the response to major abdominal surgery by extradural analgesia with local anaesthetics (Bromage, Shibata and Willoughby, 1971; Menzies Gow and Cochrane, 1979; Traynor et al., 1982; Seeling et al., 1982; Kossman et al., 1982; Tsuji, Asoh et al., 1983), but this may be explained by the inclusion of abdomino-thoracic procedures in some studies (Bromage, Shibata and Willoughby, 1971; Seeling et al., 1982) or by inadequate afferent blockade when the operation extended to the pelvis (Kossman et al., 1982). However, in the remaining studies (Menzies Gow and Cochrane, 1979; Traynor et al., 1982; Tsuji, Asoh et al., 1983) the neurogenic blockade used would have been expected to provide an adequate afferent blockade from the surgical area and, at present, we have no good explanation as to why this does not lead to the decrease in postoperative catabolism observed during surgery on the lower part of the body (Kehlet, 1982). It has been suggested that this discrepancy may be attributable to unblocked afferent vagal pathways, but infiltration of the vagus nerve with local anaesthetics immediately after opening the abdomen (Traynor et al., 1982) or an initial surgical vagotomy (Tsuji, Asoh et al., 1983) failed to potentiate the effect of extradural analgesia on the stress response. In addition, experimental studies in dogs with vagotomy, ventrolateral cordotomy or combined vagotomy plus cordotomy failed to demonstrate that the vagal afferent pathway was important for the ADH response to surgery (Ukai, Moran and Zimmermann, 1968). Therefore, the lack of a major modifying effect of extradural analgesia on the response to major abdominal surgery may be simply the result of inadequate afferent blockade compared with the strength of the stimulus from the procedure. This is supported by the fact that, although the relief of pain produced by our extradural regimen was acceptable clinically, it did not result in the total alleviation of the pain. That afferent blockade may be insufficient following a conventional extradural analgesia during major abdominal surgery was confirmed recently by the demonstration of a more pronounced inhibition of the stress response when splanchnic blockade with local anaesthetics was provided with extradural analgesia (Tsuji, Shirasaka et al., 1983). This indicates that afferent sympathetic pathways from the abdomen are important in initiating the stress response. Furthermore, the finding of differential sensitivity of A and C nerve fibres to various local anaesthetic agents may be an additional explanation of the subtotal afferent blockade—certain afferent pathways may remain relatively unblocked compared with more complete blockade of the pain conducting pathways. However, at present the data are conflicting (Cusick, Myklebust and Abram, 1980; Gissen, Covino and Gregus, 1980; Raj et al., 1982), probably because of differences in experimental models, and no definite conclusion can be drawn with regard to the degree of afferent neurogenic blockade produced by the various local anaesthetic agents in the clinical situation. Finally, we are ignorant of the relative importance of neurogenic stimuli *v.* humoral factors originating from the wound in mediating the response, although some data appear to suggest that a circulating peptide may potentiate post-traumatic proteolysis (Clowes et al., 1983).

Although our results failed to demonstrate any major influence of the extradural analgesic regimen on the endocrine response to surgery, the finding of an unaltered overall nitrogen excretion does not exclude an effect on protein metabolism. Thus, urinary nitrogen excretion represents a crude expression of protein synthesis *v.* degradation from multiple sources, thereby excluding interpretation on possible alterations in protein metabolism in selective tissues such as muscle, gut, skin etc. (Rennie and Harrison, 1984). However, the finding of a lack of influence on both the endocrine response and nitrogen excretion argues against any important effect on the catabolic response to surgery.

In conclusion, our results indicate that the provision of adequate pain relief following major abdominal surgery using an extradural analgesic regimen consisting of a local anaesthetic plus morphine does not lead to an associated decrease in the catabolic response to surgery. Possibilities of mitigating the stress response to major trauma are still limited and await an improved understanding of the physiology and the substrates involved in the transmission of nociceptive information (Yaksh and Hammond, 1982).

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EFFECT OF POSTOPERATIVE EXTRADURAL MORPHINE ON ADH SECRETION

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SUMMARY

The effect of extradural morphine on antidiuretic hormone (ADH) secretion was assessed for the first 6 h after surgery in three groups of patients. Surgery was conducted under extradural bupivacaine: thereafter patients in group I (n = 6) received further injections of bupivacaine, patients in group II (n = 6) received an extradural injection of morphine and in patients in group III (n = 5) both bupivacaine and morphine, were administered extradurally. In group I, plasma ADH values remained unchanged throughout the study. In contrast, in the two groups of patients receiving extradural morphine a delayed and stepwise increase in plasma ADH concentration was documented. These results indicate that extradural morphine induces ADH secretion and suggest that this effect is the consequence of the migration of morphine to the brainstem.

Surgery is known to disturb body water homeostasis, as a result of the hypersecretion of antidiuretic hormone (ADH) (Le Quesne and Lewis, 1953). High concentrations of plasma and urine ADH both during and after surgery have been documented previously by bio- or radioimmunoassay (Moran et al., 1964; Haas and Glick, 1978). Furthermore, it has been demonstrated that nociceptive stimulation is the main mechanism implicated in ADH hypersecretion (Moran and Zimmermann, 1967; Ukaï, Moran and Zimmermann, 1968). This ADH hypersecretion can be blocked either by extradural bupivacaine or by large doses of morphine i.v. (Philbin and Coggins, 1978; Bonnet et al., 1982).

The effect of morphine noted during surgical procedures is in sharp contrast to the stimulation of ADH secretion observed in laboratory animals following an injection of morphine (De Bodo, 1944; Vandeputte, Van Messon and Peeters, 1980). Although extradural morphine is administered frequently in the period after operation, to provide analgesia, side effects have been described—including oliguria and water retention (Bromage, Camporesi and Chestnut, 1980; Chauvin et al., 1982a). The following study was performed to assess whether extradural morphine could induce ADH secretion, and to assess if this ADH secretion could be related to morphine itself or to an incomplete blockade of neurosensory afferent pathways.

PATIENTS AND METHODS

Seventeen patients undergoing knee ligamentoplasty (performed under tourniquet) were included after informed consent had been obtained. None had any previous history of renal, cardiac, hepatic or endocrine disease. Premedication consisted of atropine 0.5 mg and diazepam 10 mg i.m. 1 h before surgery. An extradural catheter was introduced through the L2–L3 space on the arrival in the operating room and 0.5% bupivacaine 15–20 ml was injected to obtain analgesia to the T8–T10 level. An i.v. infusion of 500 ml of a colloid solution was commenced just before the induction of the extradural anaesthesia, and was followed by an infusion of an isotonic saline solution (5 ml min^{-1}) during and following the operation. At the end of the surgical procedure the patients were allocated randomly to one of three groups. In the first group (group I, $n = 6$) analgesia was maintained with 0.5% bupivacaine 10 ml injected via the extradural catheter every 2 h until the 6th hour after operation. In the second

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TABLE I. *Details of patients and duration of surgical procedure (mean±SEM)*

	Sex M/F	Age (yr)	Weight (kg)	Duration of procedure (min)
Group I	4/2	25±1.7	66±4.1	50±6.9
Group II	2/4	24±1.3	62±7.1	67±6.6
Group III	3/2	21±1.8	65±3.0	72±6.6

group (group II, $n = 6$), analgesia was produced by a single extradural injection of morphine hydrochloride 0.1 mg kg^{-1} diluted in 10 ml of isotonic saline solution and given 3 h after the last bupivacaine injection. In order to distinguish the effect of analgesia on ADH secretion from that of the specific effect of morphine, a third group (group III, $n = 5$) received both bupivacaine (as in group I) and morphine (as in group II) extradurally.

In all patients, blood samples were collected to allow measurement of plasma ADH, on arrival in the operating room but before extradural anaesthesia had been performed (t^c), at the end of the surgical procedure after either morphine or bupivacaine had been injected (t^{inj}), and then hourly for 6 h. In groups II and III, additional blood samples were withdrawn 15 and 30 min after the extradural morphine injection. Blood samples, collected in chilled glass tubes, were centrifuged within 10 min at 3000 rev min^{-1} and -4 °C for 10 min. The plasma samples were acidified to pH 4.5 with hydrochloric acid 1 mol $litre^{-1}$ in dry tubes and stored frozen at -20 °C. Plasma ADH concentration was measured in duplicate for each sample using a previously described radioimmunoassay technique (Thibonnier et al., 1981). Plasma concentrations of sodium and potassium, and plasma osmolality were ter at t^c, t^{inj} and at the 6th hour. Arterial pressure, measured by flame photometry and Fiske osmome- heart and respiratory rates and analgesia were monitored hourly during the period after operation. Pain was evaluated by the patients themselves using the scale: 0 = no pain; 1 = no pain but some discomfort; 2 = mild pain; 3 = moderate pain; 4 = severe pain; 5 = intractable pain.

Results were expressed as mean ± SEM. Statistical analysis used the Wilcoxon test for intra-group variations and the non-parametric Fisher permutation test for inter-groups comparisons.

RESULTS

Patients. Details of the patients are presented in table I. In all three groups, arterial pressure, heart rate and respiratory rate remained constant. Sodium and potassium concentrations, and plasma osmolality were not significantly different from control values during the 6 h of the study (table II).

Degree of pain. No patient complained of pain before the first extradural injection after surgery of either bupivacaine or morphine. Effective analgesia, lasting throughout the period of study, was obtained in each group, the pain score never being greater than 1 in any patient.

Plasma ADH concentration. Initial plasma ADH concentrations were identical in the three groups

TABLE II. *Arterial pressure, heart rate, plasma electrolyte concentrations and osmolality values in the three groups of patients (mean±SEM).* t^c*=control before surgery;* t^{inj}*=after operation before injection of analgesic;* t^6*=6 h after surgery*

	Arterial pressure (mm Hg)	Heart rate (beat min^{-1})	Sodium (mmol $litre^{-1}$)	Potassium (mmol $litre^{-1}$)	Osmolality (mosmol $litre^{-1}$)
Group I					
t^c	116±7.3	86±4.5	139±0.8	4.2±0.12	287±4.0
t^{inj}	112±4.1	80±5.3	141±1.6	4.5±0.2	291±4.1
t^6	112±4.5	80±4.5	139±0.4	3.9±0.13	284±2.0
Group II					
t^c	122±5.7	83±4.9	139±1.2	4.1±0.10	284±1.6
t^{inj}	120±6.9	77±7.3	141±1.2	4.4±0.12	292±2.0
t^6	106±4.5	74±4.9	138±0.9	4.2±0.13	288±2.7
Group III					
t^c	110±4.1	83±2.8	138±0.8	4.2±0.10	283±1.2
t^{inj}	114±11.4	78±8.6	138±0.8	4.4±0.12	284±1.2
t^6	106±7.1	78±7.15	137±1.3	3.9±0.13	285±4.5

TABLE III. *Plasma ADH concentrations (pg ml^{-1}) (mean±SEM) before injection (t^{inj}) and 1 h, 4 h and 6 h after the injection of bupivacaine (group I), morphine (group II), or bupivacaine plus morphine (group III)*

	t^{inj}	1 h	4 h	6 h
Group I	1.7±1.2	4.4±3.3	4.7±2.2	5.8±2.7
Group II	1.9±0.7	4.2±2.0	10.4±5.2	13.0±8.9
Group III	3.5±2.2	3.5±1.2	9.0±1.2	10.3±0.9

and were within the normal range for our laboratory (Thibonnier et al., 1981). No significant changes had occurred at the end of the surgical procedure. In group I patients (who received bupivacaine only) there were no changes in plasma ADH concentration throughout the study. In contrast, stepwise increases in plasma ADH concentration occurred in groups II and III (extradural morphine, alone or with bupivacaine) (fig. 1, table III). In these two groups, plasma-ADH concentration began to increase 3 h after the extradural morphine injection and the values measured at 4, 5 and 6 h were significantly greater than those at t^c and t^{inj}. Furthermore, the ADH concentrations observed in group III (who received morphine and bupivacaine) were significantly higher than those of group I at 4 and 5 h.

Side-effects. All patients in group I complained of leg weakness; facial itching was observed in four patients in group II and in two in group III; one patient in group II and three in group III complained of nausea; transient urinary retention was noted in four patients in group I, four patients in group II and three in group III.

DISCUSSION

Our study confirms that extradural morphine and bupivacaine produce effective analgesia after an especially painful orthopaedic surgical procedure. In addition, our results document an increase in plasma ADH concentrations under extradural morphine despite efficient analgesia. In contrast, the plasma ADH concentrations remained stable when analgesia was provided by extradural bupivacaine. The low plasma ADH values observed at the end of the surgical procedure confirm that extradural bupivacaine achieves a blockade of ADH secretion during surgery, as previously described (Bonnet et

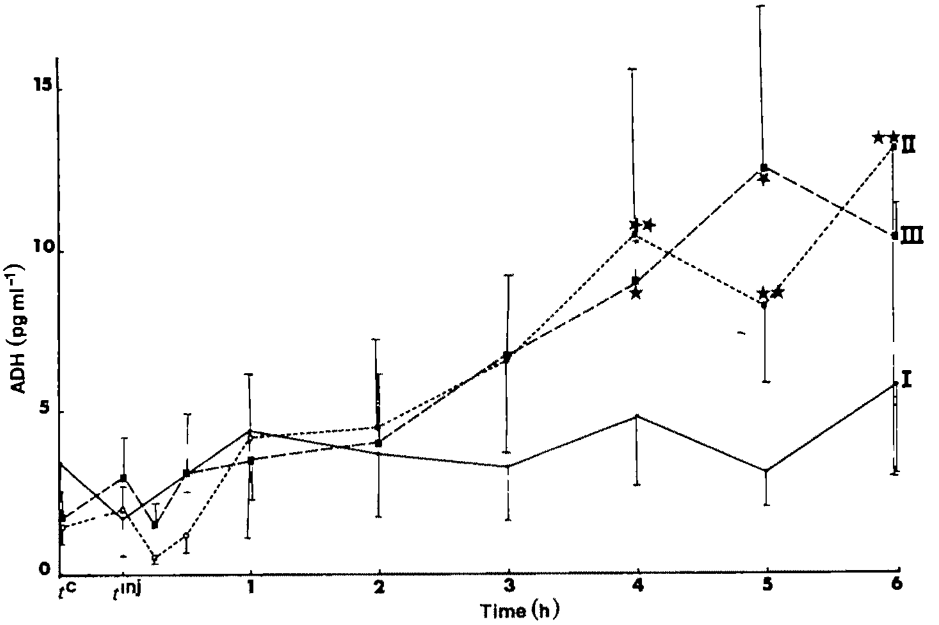

FIG. 1. Changes (mean ± SEM) in plasma ADH concentrations under extradural bupivacaine (I), morphine (II), or bupivacaine plus morphine (III). t^c = before induction of extradural blockade; t^{inj} = immediately after surgery, but before injection of analgesic. $^{**}P < 0.05$ *v.* t^{inj} values; $^{*}P < 0.05$ *v.* group I values.

al., 1982). Furthermore, the blocking effect of the extradural bupivacaine was prolonged throughout the study by repeated injections following surgery (group I patients). This effect has been demonstrated previously and attributed to blockade of afferent nervous pathways (Ukaï, Moran and Zimmermann, 1968; Bonnet et al., 1982).

Extradural morphine has been reported to induce potent, selective, long lasting analgesia (Bromage, Camporesi and Chestnut, 1980). In our study, inadequate relief of pain sedation was not the cause of the increase in plasma ADH. Other nervous pathways, such as sympathetic afferents, blocked by extradural bupivacaine, but not by morphine, could be implicated in the ADH secretion. In fact, a significant increase in plasma ADH concentrations occurred in group III patients who received both analgesic drugs. Thus, the stimulation of ADH secretion can be attributed to the extradural administration of morphine itself.

Philbin and Coggins (1978) showed that a surgically induced increase in plasma ADH concentration was partially suppressed by the administration of increasing doses of morphine. This may not necessarily conflict with our own data. In their study, very high ADH concentrations were described, but the surgical procedures involved were more major. The analgesic effect of morphine is to reduce this plasma concentration, but to a range still higher than the one we measured in our patients. In such conditions, the stimulatory effect of morphine may be masked. In contrast, stimulation of ADH secretion is produced by extradural morphine. This ADH secretion could be induced either by systemic absorption of morphine or by diffusion through the cerebrospinal fluid to the brainstem. Plasma morphine concentrations are known to increase within 15 min of extradural administration of morphine (Chauvin et al., 1982b). At that time our measurements indicate that ADH concentrations do not increase. The appearance of morphine in the cerebrospinal fluid at brainstem level is said to be delayed and thereafter to increase steadily (Drayer and Rosembaum, 1978; Bromage et al., 1982); the delayed and progressive increase in plasma ADH observed in our patients strongly suggests that ADH secretion is the consequence of migration of morphine within the CSF from the lumbar area to the brainstem.

The secretion of ADH induced by extradural morphine could be mediated by the opiate receptors located in the hypothalamus or the neurohypophysis (Simantov and Snyder, 1977). Experimental data reported in laboratory animals also suggest that β-endorphin could increase ADH secretion (Weitzman et al., 1977). However, contradictory data are reported, with the results depending on the route of administration, the nature of the opiate analogue used and the laboratory animal species studied (Van Wimersa Greidanus et al., 1978; Grossman et al., 1980; Lightman, Langdon and Forsling, 1980; Reid et al., 1981). Discrepancies in the ADH response to the administration of morphine observed during anaesthesia could be explained by different routes of administration and the effects of other causes of stimulation. Finally, this study was conducted over a relatively short period of time and no significant changes in plasma sodium concentration or osmolality were noted. However, hypersecretion of ADH could be one of the possible mechanisms behind the retention of water observed during extradural morphine analgesia.

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ZOMEPIRAC, DIHYDROCODEINE AND PLACEBO COMPARED IN POSTOPERATIVE PAIN AFTER DAY-CASE SURGERY

The relationship between the effects of single and multiple doses

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SUMMARY

Zomepirac 100 mg and dihydrocodeine 30 mg were compared with placebo in a controlled randomized, double-blind, single-dose postoperative study. Patients continued to receive either zomepirac or dihydrocodeine for pain relief for 5 days at home in a double-blind study, being allowed to titrate the consumption of tablets to their degree of pain. The efficacy and side effects of the medication were evaluated. In the single-dose phase, both active treatments were significantly better than placebo. In the multiple dosing phase, zomepirac was statistically better than dihydrocodeine. Non-parametric statistical tests indicated highly significant correlations between single- and multiple-dose analgesic measurements for both zomepirac and dihydrocodeine.

Carefully controlled and executed single-dose studies form the cornerstone of the determination of analgesic efficacy (Houde, Wallenstein and Beaver, 1965). These studies constitute a drug bioassay in man, and assay sensitivity becomes of paramount concern in trial design. However, such studies may be criticised because they are not representative of clinical practice since, in particular, the clinical use of analgesics almost always involves repeated administration. Few studies have attempted to relate the results of single dosing to the outcome following repeated administration.

To achieve this, a single-dose study must first be carried out under conditions which fulfil the usual criteria of randomized double-blind treatments, the inclusion of placebo medication to demonstrate assay sensitivity and subjective measurements of pain intensity and pain relief on clinically validated scales using a single, trained observer. Once completed, the single-dose phase should be followed by the use of medications which are active and identical in appearance to the initial dose. This satisfies the investigative and ethical requirements, since the first dose for the chronic phase may be used as medication for inadequate analgesia occurring during the single-dose phase. Correlation between the efficacy of the single and multiple doses can be sought.

The present trial was undertaken in two phases. The first was a single-dose study to assess the relative analgesic efficacy of zomepirac 100 mg by mouth, dihydrocodeine 30 mg by mouth and placebo, in the control of pain immediately following day-case surgery. In the second phase, patients were given either dihydrocodeine or zomepirac, for the management of pain following operation, for 5 days at home, and the degree of analgesia and side-effects of multiple dosing were studied. The relationship between the efficacy of the single dose and that of multiple doses was examined.

PATIENTS AND METHODS

This double-blind, parallel group study was designed as a single-dose phase followed by a multiple-dose titration phase for 5 days. Ethics committee approval was obtained to study patients undergoing elective minor day-case surgery at the Churchill Hospital, Oxford.

Seventy patients received the medication under study. Of these, only the 54 who had moderate or severe pain after surgery entered the single-dose

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phase. All 70 patients, however, were included in the 5-day multiple-dose phase. Male and female patients were selected provided that they were aged 16 yr or over and weighed between 45 and 90 kg. No patient had clinical evidence of renal, hepatic, cardiac or respiratory disease. Patients were excluded if they had been receiving regular doses of narcotic analgesics, or if they had a recent history of gastrointestinal bleeding or peptic ulceration. Women who could possibly be pregnant were excluded.

A standard anaesthetic technique was used. No premedication was given; at the induction of anaesthesia, atropine 0.6 mg i.v. was given as prophylaxis against intraoperative bradycardia and this was followed by thiopentone 5 mg kg^{-1} i.v. Anaesthesia was maintained with 67% nitrous oxide plus 1–3% halothane in oxygen. Respiration was spontaneous, with a total gas flow of 150 ml kg^{-1} min^{-1} through a Bain anaesthetic breathing system and a face-mask.

After operation all patients were transferred to the ward, where they remained until discharge later the same day. They were looked after solely by the trained, full-time nurse observer who made all the measurements.

Single-dose phase

Pain of moderate or severe intensity occurring within 2 h of recovery from anaesthesia was treated with the test medication. The treatments were block-randomized in groups of 15 and were identical in appearance. Active treatments contained either zomepirac sodium 100 mg (Zomax, Ortho Pharmaceutical, Saunderton) or dihydrocodeine 30 mg (DF118, Duncan Flockhart, Greenford, Middlesex). Tablets and containers were packed by Ortho Pharmaceutical. Each treatment consisted of two tablets so that the patients received one of the three possible treatments:

Placebo zomepirac + placebo dihydrocodeine
Placebo zomepirac + dihydrocodeine 30 mg
Zomepirac 100 mg + placebo dihydrocodeine

Before receiving the test medication, measurements of the intensity of the pain (none = 0, mild = 1, moderate = 2 and severe = 3), sedation (0 = alert, 1 = mildly drowsy, 2 = moderately drowsy and 3 = asleep), heart rate, arterial pressure and respiratory rate were obtained. These were repeated with measurements of the degree of pain relief (0 = none, 1 = slight, 2 = moderate, 3 = good and 4 = complete) at 0.5, 1, 2, 3 and 4 h. In addition, visual analogue scales (using 10-cm lines) were used to measure pain intensity, pain relief and mood at 0, 0.5, 1, 2, 3 and 4 h, together with an assessment of the pain intensity on a seven-word verbal rating scale (no pain, just noticeable, mild, weak, moderate, strong, severe and excruciating; same random word display to each patient, scored 0–7 in this order).

Volunteered side effects and their severity were noted. Any medication required before the patients left the ward that day was recorded. If no pain relief was obtained from the test medication after 1 h, or if the pain intensity reverted to initial values, the patients were given the appropriate first-blind dose of the multi-dose medication (see below). If this dose also failed to provide adequate pain relief, papaveretum 15 mg i.m. was given. Patients who received the medication and who subsequently vomited, remained in their appropriate trial group and received metoclopramide 10 mg i.m.

The sum of pain intensity difference (SPID) and total pain relief (TOTPAR) were calculated by standard procedures (Wallenstein and Houde, 1975) without stratification of the initial pain intensity values. The visual analogue equivalents, VAS-SPID for pain intensity, VAS-TOTPAR for pain relief, and the verbal rating scale equivalent for pain intensity, word-SPID, were derived in the same way as for SPID and TOTPAR. Patients who required further medication before the end of the 4-h study period were ascribed initial values of pain intensity and pain relief scores of zero (Lasagna, 1980).

The overall sedation and mood measures, $AUC_{sedation}$ and AUC_{mood} were calculated as the area under the curves of the effect against time data, using a trapezoidal formula.

Multiple-dose phase

Patients who had completed the single-dose study, and those with mild pain who did not participate in the single-dose phase, entered the multiple-dose phase. They were given medication diaries consisting of individual packets attached to sheets, with a separate sheet for each of 5 days. Day 1 was defined as the day of operation.

The multiple-dose phase was organized so that patients received either zomepirac 100 mg or dihydrocodeine 30 mg for the whole of the 5 days. The packets were identical in appearance and each contained two tablets, either zomepirac 100 mg and placebo dihydrocodeine or placebo zomepirac and dihydrocodeine 30 mg. Patients were instructed to tear off a single packet from the sheet for the appropriate day as analgesia was needed; a total of 30 medications was provided. As a measure of compliance, the patients were asked to record the time at which the dose was taken and the pain intensity at that time.

Patients who had received active zomepirac or active dihydrocodeine in the single-dose phase continued on the same drug for the multiple-dose phase. Those who had received placebo, or who had only mild pain and who did not enter the single-dose phase were randomly assigned to one of the two treatment groups.

The patients were interviewed on days 2 and 5 of the study. On day 2 they were questioned about the intensity of pain during the first night after operation, scored on a four-point scale (0 = none; 1 = slight; 2 = moderate; 3 = severe), and the adequacy of sleep was scored on a five-point scale (0 = poor; 1 = fair; 2 = good; 3 = very good; 4 = excellent). Additionally, they were questioned about the presence or absence of problems with micturition or mobility. Volunteered side effects were noted.

On day 5 the patients were questioned about their experience since the operation. The following aspects were investigated using categorical scales: the worst pain intensity (0 = none; 1 = slight; 2 = moderate; 3 = severe); best pain relief (0 = none; 1 = slight; 2 = moderate; 3 = good; 4 = complete); global impression of the tablets, appetite, mobility and sleeping (0 = poor; 1 = fair; 2 = good; 3 = very good; 4 = excellent). They were also questioned about problems with micturition and about bowel habit. Volunteered side effects were recorded. At this same visit the medication diaries were collected, and the drug consumption for each of the five treatment days recorded.

Statistical analyses for the analgesic measures and demographic data were by the Kruskal–Wallis one-way analysis of variance and Student's *t* test. The incidence of side effects and need for additional analgesia were analysed by the Chi-square test.

Single- and multiple-dose analgesic measures were compared within the patient for those patients receiving active treatments in the single-dose phase by Spearman's rank correlation. Correlations were obtained separately for zomepirac and dihydrocodeine, four correlations being studied:

(1) Single-dose SPID:worst pain on first night after operation

(2) Single-dose SPID: best pain relief score (5 days)

(3) Single-dose SPID: total tablets consumed over 5 days

(4) Single-dose SPID: best pain relief score/total tablets.

TABLE I. *Demographic data for single-dose phase (mean values*±SEM). *There were no statistically significant differences between the groups, using the Kruskal–Wallis and Chi-square tests as appropriate*

	Placebo	Dihydrocodeine	Zomepirac
No. patients	19	18	18
Female:Male	6.13	10:8	7:11
Age (yr)	44.0±3.8	44.1±3.2	44.6±4.0
Weight (kg)	72.7±2.8	66.0±2.4	69.7±2.0
Height (cm)	173.0±2.9	168.0±1.8	171.7±2.0
Girth (cm)	89.6±2 4	87.7±1.9	85.0±5.3
Duration of surgery (min)	37.1±3.71	33.6±2.8	34.8±2.8
Overnight hospital stay (Yes:No)	4:15	2:16	1:17
Smokers (Yes:No)	10:9	4:14	6:12
Operation type			
Hernia	10	9	6
Veins (high tie)	2	2	3
Veins (low only)	2	5	4
Circumcision	1	0	3
Rectal polyp/ haemorrhoid	2	0	0
Zadeck's	0	1	0
Breast lump	0	1	0
Hydrocele/E cyst	0	0	2
Mandibular cyst	1	0	0
Ganglion	1	0	0

The Mann–Whitney *U* test was used to compare tablet consumption, global relief and best relief in patients stratified by single-dose SPID values.

RESULTS

Single-dose phase

The demographic data for the patients in the three groups in the single-dose phase of the study are shown in table I. The groups did not differ significantly for age, weight, height, girth, duration of operation (Kruskal–Wallis one-way analysis of variance), the proportion of smokers to non-smokers or for patients who remained in the ward overnight (Chi-square test). The spectrum of operative procedures was similar in all groups.

The time course of analgesia was similar in all three groups. Figure 1 shows the mean visual analogue pain relief scores: for the active treatments, maximum pain relief occurred at about 2 h, and did not decline significantly over the remainder of the study period. Zomepirac 100 mg produced about 60% of maximum pain relief at this time, while dihydrocodeine 30 mg produced about 47% and placebo about 32%. At 2 and 3 h the zomepirac (but

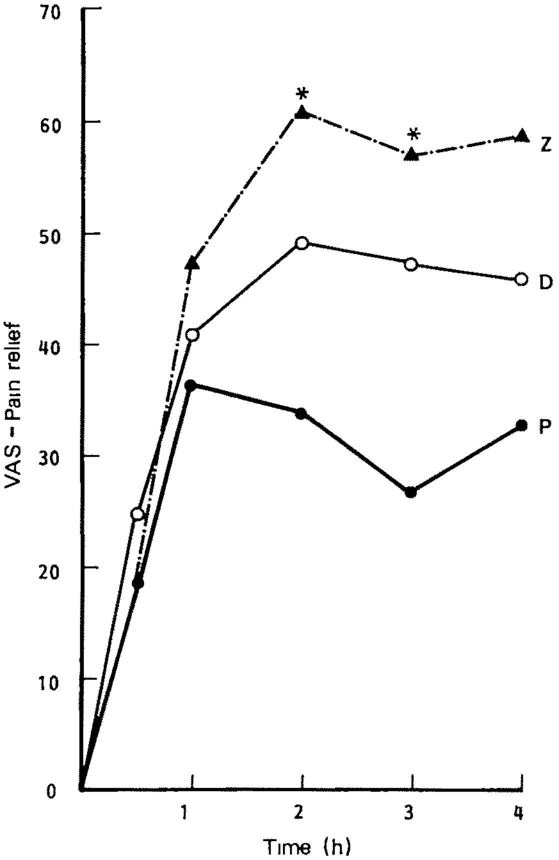

FIG 1. Mean visual analogue pain relief scores for patients receiving zomepirac 100 mg (Z), dihydrocodeine 30 mg (D) and placebo (P). *Significantly different ($P < 0.05$) from placebo, Student's *t* test.

not the dihydrocodeine) scores were significantly higher than placebo ($P < 0.05$, Student's *t* test).

For the integrated analgesic measurements (table II), Student's *t* test demonstrated that the dihydrocodeine group had significantly more analgesia than placebo using TOTPAR ($P < 0.05$) and VAS-SPID ($P < 0.01$) scales. Patients given zomepirac 100 mg demonstrated significantly better analgesia than placebo on all five scales: SPID ($P < 0.02$), TOTPAR ($P < 0.02$), VAS-SPID ($P < 0.01$), VAS-TOTPAR ($P < 0.02$), and word-SPID ($P < 0.01$). These results were supported by significant differences for VAS-SPID, VAS-TOTPAR and word-SPID using the Kruskal–Wallis test (table II).

For none of these measures was the analgesia produced by zomepirac 100 mg statistically better than that produced by dihydrocodeine 30 mg, although in each case the tendency was for more analgesia with zomepirac. There was no significant difference in the $AUC_{sedation}$ or AUC_{mood} scores for the three groups.

In all three groups, some patients required further analgesia during the study period (table II). Fifteen of the 19 patients in the placebo group required an analgesic, mostly within the first hour of the study. This proportion was significantly greater than in the two treatment groups ($P < 0.02$, Chi-square test). Very few patients required papaveretum (two in the dihydrocodeine group, one in the zomepirac group and three in the placebo group).

The number of reported side effects was small (table III), with no statistically significant differences between the three groups of patients.

TABLE II. *Single-dose analgesic measurements (mean values±SEM). K is the degree of significance obtained between the groups using the Kruskal–Wallis test. Significant difference from placebo:* *$P<0.05$, **$P<0.02$, ***$P<0.01$ *(Student's t test);* †$P<0.02$ *(Chi-square test)*

	K	Placebo	Dihydrocodeine 30 mg	Zomepirac 100 mg
No. patients		19	18	18
SPID	ns	1.0±0.54	2.5±0.54	3.1±0.59**
TOTPAR	ns	3.2±1.07	6.5±1.17*	7.6±1.26**
VAS-SPID	<0.05	25.6±10.6	99.6±22.0***	102.4±19.4***
VAS-TOTPAR	<0.05	84.7±28.2	166.5±31.8	200.4±33.8**
Word-SPID	<0.05	2.4±0.96	4.9±1.16	6.8±1.28***
$AUC_{sedation}$	ns	3.7±0.8	4.6±0.8	4.1±1.0
AUC_{mood}	ns	329±30	406±28	405±38
No additional medication†		4	9	11

TABLE III. *Side-effects during single-dose phase. No significant differences between the groups (Chi square test)*

	Placebo	Dihydrocodeine 30 mg	Zomepirac 100 mg
No. patients	19	18	18
Total No. patients affected	3	6	3
Headache	3	2	2
Dizziness	0	1	1
Confused	0	1	0
Nausea	0	2	1

Multiple-dose phase

Demographic data on the two groups of patients who entered the multiple-dosing phase of the trial are shown in table IV. No statistical differences were observed, except for smoking. In particular, there was no statistically significant difference between the two groups for drug consumption over the 5 days. The number of tablets consumed was comparable over the first 4 study days, and it was only on day 5 that a significant reduction in analgesic requirement occurred ($P < 0.001$, unpaired Student's *t* test).

Even though patients were allowed to consume sufficient tablets to control their pain, significant differences between the groups for some retrospective pain measures were found at the 2nd and 5th days (table V). On day 2, the patients receiving zomepirac had significantly ($P < 0.05$, Student's *t* test) less pain at night, and slept better ($P < 0.05$) than did those receiving dihydrocodeine.

TABLE IV. *Demographic data and drug consumption for multiple-dosing phase (mean values±SEM). There were no statistically significant differences between the groups using the Kruskal–Wallis, Student's* t *test, or Chi-square test, as appropriate. *Significant reduction in analgesic consumption from day 1 (*P<0.001*, Student's unpaired* t *test)*

	Dihydrocodeine 30 mg	Zomepirac 100 mg
No. patients	34	36
Female:Male	17:17	13:23
Age (yr)	44.4±2.4	42.3±2.5
Weight (kg)	69.3±1.8	69.8±1.6
Height (cm)	168.7±1.8	173.0±1.9
Girth (cm)	89.2±1.5	85.6±2.8
Duration of surgery (min)	33.0±2.1	36.5±2.4
Smokers (Yes:No)	10:24	26:10
Analgesic consumption		
Day 1 total tablets	2.0±0.17	1.9±0.14
Day 2 total tablets	2.7±0.34	2.8±0.25
Day 3 total tablets	2.4±0.36	2.1±0.25
Day 4 total tablets	1.8±0.35	1.4±0.26
Day 5 total tablets	0.6±0.16*	0.6±0.13*
Overall total tablets	9.5±1.21	8.8±0.88

TABLE V. *Analgesic measurements during multiple-dosing phase (mean±SEM). Statistically significant differences between the groups, Student's* t *test: **P<0.05*, ***P<0.02*, ****P<0.01*

	Dihydrocodeine	Zomepirac
No. patients	34	36
Day 2		
Worst pain in night	1.5±0.18	1.0±0.15*
Sleep adequacy	1.6±0.20	2.3±0.23*
Day 5		
Worst pain	2.7±0.10 (*n*=32)	2.4±0.10
Best relief	2.7±0.19 (*n*=32)	3.4±0.14***
Global impression of tablets	2.3±0.22 (*n*=29)	2.9±0.17** (*n*=35)
Mobility	1.7±0.18 (*n*=31)	1.9±0.13
Appetite	1.6±0.20 (*n*=31)	2.3±0.19**
Sleep	2.2±0.23 (*n*=31)	2.4±0.18

On day 5, although there was no difference for the worst pain experienced, significantly ($P < 0.01$) better relief of that pain was reported by the zomepirac group. In addition, they reported better appetite ($P < 0.02$), but no better mobility than the dihydrocodeine group, and no improvement in the quality of sleep as there had been on day 2. Overall, the zomepirac group had a significantly better global impression of their tablets ($P < 0.02$) than those taking dihydrocodeine.

The volunteered side effects reported by the patients on the 2nd day, and retrospectively over the whole 5 days, are shown in table VI. The only significant difference between the groups was for the change in bowel habit noted at 5 days; dihydrocodeine produced significantly more constipation ($P < 0.02$, Chi-square test). Over the whole period, slightly more than half the patients in each group experienced side effects, although there was no significant difference between the total number of patients affected in each group.

Relation of single- to multiple-dose effects

Single-dose SPID:worst pain on first night after operation. There was no significant correlation between the single-dose SPID and the worst pain measure on the first night after operation (correlation coefficient = 0.06 for dihydrocodeine

TABLE VI. *Side effects during multiple-dose phase.* **P<0.02, Chi-square test

	Dihydrocodeine	Zomepirac
On day 2		
No. patients	34	36
Total No. patients affected	14	9
Constipation	1	0
Dizziness	2	1
Nausea	6	6
Headache	2	0
Drowsiness	4	2
Appetite change	1	0
Vomiting	1	2
Abdominal pain/indigestion	0	1
Thirsty	0	1
Immobility (Yes:No)	3:31	0:36
Micturition problems (Yes:No)	2:32	1:35
Over whole 5 days		
No. patients	34	36
Total No. patients affected	18	19
Dizziness	2	3
Nausea	7	6
Headache	2	2
Drowsiness	12	8
Appetite change	1	0
Vomiting	0	1
Abdominal pain/indigestion	0	3
Thirsty	3	5
General malaise	2	1
Micturition problems (Yes:No)	4:30	1:35
Bowel problems (Yes:No)	20:15	10:26**

= 18) and −0.10 for zomepirac ($n = 18$).

Single-dose SPID:best pain relief score (5 days). The correlation between the single-dose SPID and the best relief scores on the 5th day of the multiple-dose phase gave a coefficient of 0.74 for dihydrocodeine ($n = 17$) and 0.40 for zomepirac ($n = 18$) ($P < 0.001$ and <0.1, respectively, Spearman rank test).

Single-dose SPID:total tablets consumed over 5 days. There was no significant correlation between the single-dose SPID and the total tablet consumption for the 5 days (coefficient = −0.34 for dihydrocodeine ($n = 18$) and −0.12 for zomepirac ($n = 18$)).

Single-dose SPID:best pain relief score/total tablets. The correlation between the single-dose SPID and the best relief scores on day 5 divided by total tablet consumption in the multiple-dose phase was 0.596 for dihydrocodeine ($n = 17$) and 0.468 for zomepirac ($n = 18$) ($P < 0.05$ in both cases, Spearman rank test).

This was supported by examining the scores for best relief and global impression for the patients with the largest and the smallest values for SPID in the single-dose phase. The 5-day values for best relief were significantly larger for patients with highest single-dose SPID (3.7 ± 0.2, $n = 14$, *v.* 2.1 ± 0.4, $n = 11$; $P < 0.02$, Mann–Whitney U test); similarly, the same patients had a better global impression of the tablets (3.2 ± 0.25 *v.* 1.9 ± 0.41, $P < 0.05$, Mann–Whitney U test). The patients who had the least pain relief on single dosing consumed significantly more tablets during multiple dosing than did those with the best relief (12.5 ± 1.8 *v.* 7.4 ± 0.8, $P < 0.02$, Mann–Whitney U test).

DISCUSSION

This study was designed to answer the question "How effective are single-dose studies in predicting analgesic effect and the incidence of side-effects when the same medications are taken in multiple dosage?" A valid single-dose phase was required from which correlations could be made into the multiple-dose phase.

The single-dose phase of this study compared zomepirac 100 mg, dihydrocodeine 30 mg and placebo and great sensitivity was shown, dihydrocodeine being differentiated from placebo on two, and zomepirac on all of the five analgesic measures. In addition the Kruskal–Wallis test was significant for VAS-SPID, VAS-TOTPAR and word-SPID. Zomepirac 100 mg scored better on all the measures than did dihydrocodeine 30 mg, but the scores could not be distinguished statistically.

A similar trend was found for chronic administration. Even though the numbers of tablets consumed by patients in the zomepirac and dihydrocodeine groups were the same, zomepirac was significantly better for worst night pain and adequacy of sleep on day 2, and for best relief, appetite and global impression over the whole 5 days. The single and multiple-dosing phases of the trial gave a similar impression, therefore, and supported each other.

Patients usually take drugs in multiple doses. How useful, then, are estimates of the incidence of side-effects and their type and severity from single-dose studies? Multiple doses of zomepirac in patients with chronic back pain produced side-effects in some patients sufficient to make them discontinue the tablets, despite the fact that they were still obtaining analgesia (Evans, Carroll et al., 1982). A single-dose postoperative study of the same drug produced few side-effects (Evans, McQuay et al., 1982). The predictive value of the single-dose phase in this study for side effects on multiple dosing was also poor. There were very few side effects with the single dose, but about half the patients volunteered some side effect after 5 days with an average consumption of about 2 tablets a day.

Patients in the multiple-dose phase were instructed to take as many as they required of the six available doses each day. The intention was that they should titrate themselves to optimal analgesia, rather than maintain a fixed dose schedule. The single-dose phase SPID value was then correlated to multiple-dose phase analgesic measures in four different ways for both zomepirac and dihydrocodeine.

There was no significant correlation to the worst pain on the first night after operation. Satisfactory analgesia from the first dose after operation did not preclude severe pain early in the course of multiple dosing.

The correlation of single-dose SPID to best relief score at 5 days was significant for both drugs. The correlation coefficient for dihydrocodeine was greater than that for zomepirac, although the number of patients with maximum best relief scores was greater in the zomepirac group. This raises an important methodological issue. The 5-day indices available for correlation were limited to simple categorical scales of 5 points. Consequently, there were problems of tied scores, especially for the zomepirac group where very high values for best relief were the rule. The effect of such tied scores is to decrease the significance of the correlation, although the drug gave highly effective multiple-dose phase analgesia.

There was no significant correlation between single-dose SPID and total tablet consumption over the 5 days. Patients with poor analgesia (low SPID) on the single-dose phase should have needed more tablets in the multiple-dose phase and the converse would be expected for those with high single-dose SPID values. This proved to be the case for the extremes: stratification into best (3) and worst (0) SPID showed significantly better retrospective pain relief and global impression, as well as lower tablet consumption in the high SPID group. The explanation of the overall insignificant correlation for both drugs in this study may be that patients were unable to keep on increasing the number of doses because of the occurrence of side effects.

Dividing the relief score by the number of tablets then weights the relief score appropriately, because the influence of side effects in making an increase in dose impossible is countered. The correlation between single-dose SPID and best relief (5 days) divided by tablet consumption proved significant for both dihydrocodeine and zomepirac.

Postoperative analgesic practice has been criticised (Editorial, 1976). Interindividual differences for analgesic requirement (Bullingham et al., 1981; Jacobs, et al., 1981; McQuay et al., 1982) are one cause of failure. An estimate of a patient's need may be obtained by studying the clinical response to a standard prescription of postoperative analgesia (Church, 1979). Response to the first prescribed analgesic as a rationale for further prescription requires validation of the predictive value of the single-dose effects for multiple dosing.

In circumstances such as day-case surgery where the patient must cope with further analgesic requirements at home, the predictive necessity of the single dose is highlighted. In this study, the correlation of analgesic effect was good; essentially, those with poor analgesia from active medication on the single dose needed more tablets over the whole 5-day period and in general fared worse. This suggests that a simple clinical method to identify this group would improve their care after operation. Importantly, the incidence of side effects following the single dose was not a true reflection of the incidence on multiple dosing, and the increase in incidence prevented patients from taking an adequate number of doses to relieve their pain.

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PORPHYRINOGENICITY OF ETOMIDATE AND KETAMINE AS CONTINUOUS INFUSIONS

Screening in the DDC-primed Rat Model

G. G. HARRISON, M. R. MOORE AND P. N. MEISSNER

SUMMARY

The porphyrinogenicity of etomidate and ketamine administered as continuous i.v. infusions was screened in the DDC-primed rat model of latent variegate porphyria. Ketamine produced no change from control in 5-aminolaevulinate synthase (ALAs) activity and haem intermediate production in either untreated or DDC-primed rats, and would appear to be safe for use in the patient with genetic porphyria. Etomidate, while producing no significant changes in these parameters in untreated rats, caused a statistically significant 47% increase in hepatic ALAs activity with a corroborative 85% increase in coproporphyrin and a 40% increase in protoporphyrin content, in DDC-primed rats. On these grounds, etomidate must be regarded as potentially porphyrinogenic when administered as a continuous infusion for total i.v. anaesthesia.

The acute porphyrias are a group of inherited metabolic diseases, acute attacks of which are often triggered by the use of certain drugs (Moore and Disler, 1983). Prevention of life-threatening crises of acute porphyria in genetically susceptible individuals depends on identification of those individuals, and identification of porphyrinogenic drugs. In the past, information on the latter was largely anecdotal, but additional objective evidence can now be obtained by observing, in liver homogenates of experimental animal models, the effects of the drug in question on 5-aminolaevulinate synthase (ALAs) activity and the production of the haem biosynthetic porphyrin intermediates (Parikh and Moore, 1978; Blekkenhorst et al., 1980).

Prominent among known porphyrinogenic drugs are the barbiturates most commonly used for induction of general anaesthesia. Of the recently introduced i.v. anaesthetic induction agents, two (Althesin and flunitrazepam (Rohypnol)) have now also been incriminated, while animal screening of a third (etomidate) has produced results that are suggestive of porphyrinogenicity (Disler et al., 1982). Parikh and Moore (1978) also had concluded that this drug was porphyrinogenic, following their demonstration in the rat that repeated i.p. doses of etomidate caused an increase in hepatic ALAs activity. However, in the study of Blekkenhorst and colleagues (1980), in the 3,5-dicarbethoxy-1,4-dihydrocollidine (DDC)-primed rat model which simulates latent variegate porphyria, the mean increase in hepatic ALAs activity that followed single dose i.p. administration of etomidate just failed to achieve statistical significance. In humans, no corroborative examples of acute porphyria precipitated by etomidate have yet been reported.

The short disposal half-life of etomidate makes it particularly suitable for use not only for i.v. induction of general anaesthesia when administered as a single dose, but also for total i.v. anaesthesia when administered as a continuous i.v. infusion. In view of this and the above findings, it seemed to us important to extend the screening of etomidate for porphyrinogenicity from single dose administration to continuous i.v. infusion in the DDC-primed rat model.

Control conditions of total i.v. anaesthesia were produced by continuous infusion of ketamine, a drug generally regarded as non-porphyrinogenic

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(Disler et al., 1982).

METHODS

Male Wistar rats (weight 200–300 g) were submitted to i.v. anaesthesia for 6 h by continuous infusion of the test drug to a cannulated femoral vein by means of a mechanically driven syringe pump.

Twelve rats were anaesthetized with etomidate and 12 with ketamine, the dose of anaesthetic having been established empirically as that which maintained adequate depth of anaesthesia without causing anaesthetic death. With etomidate, 4 mg i.p. was adequate for anaesthesia for femoral vein cannulation, whereafter anaesthesia was maintained by continuous i.v. infusion of 10–15 mg kg^{-1} h^{-1}. With ketamine the doses were 100 mg kg^{-1} i.p. and 10–15 mg kg^{-1} h^{-1}, respectively. Both drugs were diluted so that the volume of fluid administered approximated 2 ml h^{-1}.

Spontaneous respiration of air was maintained throughout anaesthesia. Experiments were conducted using pairs of rats one from each group anaesthetized simultaneously. Six animals in each group were treated for 3 days before anaesthesia with DDC administered orally at a dose of 50 mg kg^{-1} dissolved in 1 ml of corn oil. All animals were starved for 24 h before anaesthesia, but were permitted water *ad libitum*.

After 6 h of anaesthesia, animals were sacrificed and their livers removed, blotted free of blood and washed with ice-cold saline. Hepatic ALAs activity was assayed and full porphyrin analysis of hepatic homogenates carried out.

Assays

ALAs activity was measured by the method of Moore and others (1980), in which the production of ^{14}C-labelled ALA from ^{14}C-labelled glycine is measured after separation of ALA by high voltage electrophoresis. Incubations were carried out using liver homogenate at 37 °C for 1 h.

Porphyrin analysis. Porphyrins were measured, using HPLC, by the method of Seubert and Seubert (1982). The methyl esters of porphyrins used as standards were obtained from Porphyrin Products (Logan, Utah) and dissolved in chloroform. The separations were performed on a Waters liquid chromatograph with a Model 6000-A solvent delivery system, a Model 710-B WISP automatic injector, a Model RCM-100 module and Radial-PAK silica cartridges, 10-μm particle size and a Model 420-AC fluorescence detector (Waters Associates, Milford, Mass.). The chromatograms were evaluated with a Waters Model 730 Data Module.

Liver samples for porphyrin analysis were prepared as follows: known weights of liver were esterified overnight, in the dark at room temperature in 10 volumes of 5% sulphuric acid in methanol solution. After centrifugation the supernatant was neutralized with 5% ammonia solution in a separating funnel where the porphyrin esters were extracted into chloroform, washed with distilled water and dried by draining over anhydrous sodium sulphate. Before injection to the chromotograph, each sample was evaporated to dryness in a Bucchi rotary evaporator and redissolved in exactly 1 ml of chloroform.

TABLE I. *Untreated rats anaesthetized for 6 h with ketamine or etomidate. No value was significantly different from control (unanaesthetized)*

	ALAs (mmol h^{-1}/g protein)	Uroporphyrin (mmol/g liver) (wet)	Coproporphyrin (mmol/g liver) (wet)	Protoporphyrin (mmol/g liver) (wet)
Unanaesthetized				
n	12	3	3	3
Mean	57.5	0.0075	0.2314	0.8046
SD	21.0	0.0044	0.1116	0.0814
Ketamine				
n	6	5	5	5
Mean	53.0	0.02672	0.2193	0.7613
SD	22.0	0.0450	0.1293	0.1936
Etomidate				
n	6	5	5	5
Mean	69.0	0.0487	0.2975	0.9115
SD	12.0	0.0584	0.1000	0.2936

TABLE II. *DDC-primed rats anaesthetized for 6 h with ketamine or etomidate.* **Significant difference from control (unanaesthetized)*

	ALAs (mmol h^{-1}/g protein)	Uroporphyrin (mmol/g liver) (wet)	Coproporphyrin (mmol/g liver) (wet)	Protoporphyrin (mmol/g liver) (wet)
Unanaesthetized				
	6	3	3	3
Mean	426.1	0.0271	0.679	9.2536
SD	122.3	0.0238	0.1709	1.0582
Ketamine				
n	6	5	5	5
Mean	473.0	0.0544	0.6950	9.1044
SD	77.0	0.7123	0.2799	1.0369
Etomidate				
n	6	5	5	5
Mean	625.0	0.2869	1.2598	12.9715
SD	105.0	0.2666	0.4452	1.3720
P*	<0.02	ns	<0.05	<0.01

Control data were obtained from similar assays undertaken on six unanaesthetized rats, half of which were pretreated with DDC. The significance of differences between sample means was established by means of Student's t test.

RESULTS

Anaesthesia with ketamine caused no significant change when compared with unanaesthetized controls in either untreated (table I) or DDC-primed (table II) rats. Hepatic ALAs activity and porphyrin content were the same in both groups.

By contrast, 6 h of etomidate anaesthesia, which produced no change from control in untreated animals (table I), caused a marked increase in all these parameters in DDC-primed rats (table II, fig. 1). The 47% increase in hepatic ALAs activity and corresponding 85% increase in coproporphyrin and 40% increase in protoporphyrin content were statistically significant. The almost 10-fold increase in uroporphyrin failed to achieve statistical significance because of the large variance in the values.

DISCUSSION

The essential criterion for judging the porphyrinogenicity of a drug in the DDC-primed rat model of latent variegate porphyria is a demonstrable increase in hepatic ALAs activity in response to administration of the drug (Blekkenhorst et al., 1980). On these grounds we must infer from our experiments that etomidate is potentially porphyrinogenic. The 47% increase in ALAs activity observed in response to etomidate was accompanied by a corroborative increase in resultant haem precursors. The failure of the observed increase in uroporphyrin to achieve statistical significance reflects the large variation in haem precursor

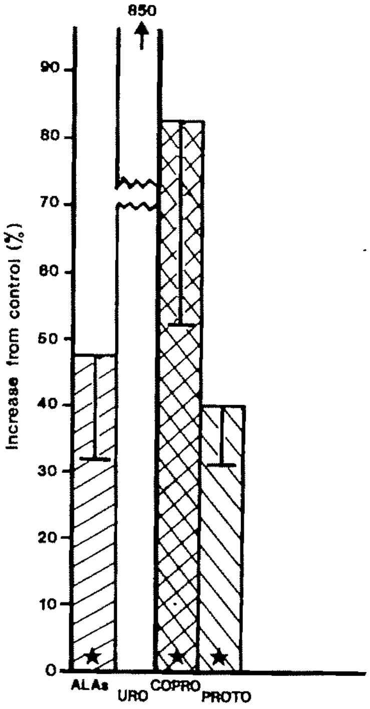

FIG 1. Effect of a 6-h infusion of etomidate on 5-aminolaevulinate synthase (ALAs) activity and haem intermediates in DDC-primed rats. 0 = control. URO = uroporphyrin; COPRO = coproporphyrin, PROTO = protoporphyrin. ★Significantly different from control. Vertical bar = standard error of difference

response to drug administration, previously observed by Eales and Blekkenhorst (1978), and the small numbers of animals used in the present trial.

Identification of a porphyrinogenic drug in an animal model is far removed from proof that it is potentially dangerous to the human sufferer from genetic hepatic porphyria. We identify only that, in this particular animal model, the drug in question displays a property known to characterize those drugs which do precipitate crises in susceptible humans. Drug metabolism differs profoundly between species, and even animals so apparently similar as rats and mice display marked variation in the response of their haem biosynthetic pathway to the effects of various drugs.

Final proof of the porphyrinogenicity of a drug should come from a clinical report of the initiation of an acute crisis in a susceptible individual following exposure to the drug. Regrettably, even this premise may be false—there are well documented inconsistencies.

Disler and colleagues (1982) devised the following simple classification of drugs to guide clinicians in the assessment of porphyrinogenicity:

Category A	Drugs reported in terms of clinical experience as dangerous or safe by three or more authorities.	Associated with corroborative experimental animal data
Category B	As above but only two or fewer authorities.	
Category C	Drugs evaluated only in the experimental rat model.	No corroborative reports of human cases
Category D	Drugs evaluated in chick embryo liver cell culture or "*in ovo*".	

On the basis of our present observations and those of Parikh and Moore (1978), etomidate qualifies for a "C" rating. From this we infer that, although its use in susceptible individuals cannot be definitely contraindicated, it should be so used only when no convenient alternative is available. Thereafter, the patient should be observed and appropriately screened for a period, using biochemical tests, in order to detect any nascent crisis in good time.

Although ketamine has been implicated as porphyrinogenic in a single case report (Wetterberg, 1976), it is considered safe by many authorities (Rizk, Jacobson and Silvay, 1977; Parikh and Moore 1978; Silvay, Miller and Tausk, 1979). Our present study supports this belief in its safety for use in the patient with porphyria.

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NEUROLOGICAL TOXICITY OF THE SUBARACHNOID INFUSION OF BUPIVACAINE, LIGNOCAINE OR 2-CHLOROPROCAINE IN THE RAT

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SUMMARY

Neurotoxicity after subarachnoid infusion of bupivacaine, lignocaine and 2-chloroprocaine was studied in a chronic rat model. Hartmann's solution 100 $\mu l\ h^{-1}$ was infused as a control, and 0.5% bupivacaine, 1.5% lignocaine and 2.0% 2-chloroprocaine were infused at 100 $\mu l\ h^{-1}$ for 3, 6 or 24 h, to five rats in each group. No residual paralysis occurred in the control group, but 27 of 45 rats (60%) which received an infusion of local anaesthetic had residual paralysis lasting until sacrifice at 7 days. The incidence of paralysis was dependent on the duration of exposure to the local anaesthetic, but there were no significant differences in incidence between any of the local anaesthetics tested. Abnormal histology, in the form of neuronal vacuolation, was not a sensitive index, being present in control rats, but more intense in those receiving lignocaine and 2-chloroprocaine than in those given bupivacaine; no correlation with clinical findings could be established. The neurotoxic effects of each local anaesthetic tested as a continuous intrathecal infusion were dose related in the rat, which may be a useful model for screening other local anaesthetics.

Neurological deficit after administration of local anaesthetics is a potential complication of extradural or spinal anaesthesia. Previous animal studies reported on the neurotoxic effects of a single bolus injection of a large volume of local anaesthetics to the subarachnoid space (Ravindran, Turner and Muller, 1982; Rosen et al., 1983). Artefacts determining the methodology included traumatic injury to the spinal cord and the need for prolonged cardiovascular and ventilatory support, which might affect perfusion of the spinal cord.

At present there is interest in the use of continuous infusions of local anaesthetics for extradural analgesia but, with this method, the safety of nervous tissue constantly exposed to local anaesthetics which may be accidentally infused intrathecally, remains to be established. The present experiments were performed on unanaesthetized, mobile rats to study the neurological sequelae of intrathecal infusion of bupivacaine (Marcain), lignocaine (Xylocaine), 2-chloroprocaine (Nesacaine-CE) and Hartmann's Solution (Travenol). All solutions were free of preservative.

MATERIALS AND METHODS

Preparation of rats

Three to five days before the experiment, the subarachnoid spaces of 50 Wistar rats (180–240 g) were cannulated with fine polyethylene tubing (Portex) via the lumbar vertebrae as previously reported (Bahar, Rosen and Vickers, 1984). The location of the catheter was confirmed by injecting 2% lignocaine 35 µlitre, which invariably paralysed both hind limbs of the rat and conferred lumbar analgesia. Those rats in which there was any doubt about the location of the catheter or which showed any evidence of traumatic nervous damage were not included in the experiment.

Plan of investigation

On the day of the experiment, a jacket was put on the rat which was under inhalation anaesthesia

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(2.5% halothane in oxygen 250 ml min^{-1}). The intrathecal cannula was passed through a swivel clamped to the cage and connected to a syringe pump. The whole system was protected by a lightweight metal tether (Harvard Apparatus). The animal recovered from anaesthesia and was fully mobile.

Five rats were randomly allocated to each of 10 groups receiving an intrathecal infusion at 100 μl h^{-1}:

Group 1: Control group with Hartmann's solution (pH 5.93–6.29) for 24 h.

Groups 2–4: 0.5% Bupivacaine (pH 5.56–5.63) for 3, 6 and 24 h, respectively.

Groups 5–7: 1.5% Lignocaine (pH 5.15–5.19) for 3, 6 and 24 h, respectively.

Groups 8–10: 2.0% 2-Chloroprocaine (pH 2.90–3.05) for 3, 6 and 24 h, respectively.

All drugs were free of preservative with no adrenaline, and the local anaesthetics consistently paralysed both hind limbs but left the front limbs mobile.

During the period of infusion all rats were free to move, with access to food and water. After the designated period the infusion was disconnected and the rats returned to separate cages, where they were examined daily for any residual neurological deficit, for 7 days before sacrifice for pathological examination.

Histology

Immediately after the rat was killed, 500 μlitre of 10% formalin was injected slowly through the intrathecal catheter. The vertebral column was then removed in one piece and fixed in 10% formalin in saline for 2 days. The specimen was then decalcified for 1 week. Sections of the spinal cord were taken from the region adjacent to the tip of the catheter, which should have been subjected to the maximum effects of the drugs. Sections were embedded in paraffin, cut at 5-μm intervals and stained with haematoxylin and eosin (H/E) and Kluver-Barrera stain (KLB) for myelin. Microscopic examination was carried out by a neuropathologist (G.C.) who was unaware of which drug had been infused.

Statistical analysis was by Chi-square test.

RESULTS

Clinical findings

Apart from the group receiving Hartmann's solution, a steady block with lumbar analgesia and paralysis of both hind limbs were observed in all rats receiving local anaestheic, throughout the infusion.

No residual neurological deficit occurred in the group receiving Hartmann's solution (table I). Of the 45 rats which received an infusion of local anaesthetic, 27 had residual paralysis of at least one hind limb, usually the right one: nine in the bupivacaine groups, eight in the lignocaine groups and 10 in the 2-chloroprocaine groups (table I). The neurotoxic effects were dose dependent and related to the duration of exposure: 13 of 15 which received the infusion for 24 h and 10 of 15 which received the infusion for 6 h, but only four of 15 which received the infusion for 3 h were paralysed ($\chi^2 = 11.667$, $P < 0.005$). No difference was observed between the effects of the three local anaesthetics ($\chi^2 = 0.556$, ns).

Histological findings

In all animals, the white matter showed spongiose changes, but no obvious cellular reaction. This appearance was present in control animals, and was therefore probably an artefact related to the method of fixation. The grey matter of some animals showed varying degrees of intra- and perineuronal vacuolation (fig. 1), the occurrence of which was more common in the lignocaine and 2-chloroprocaine groups than in the bupivacaine groups (tables II and III) ($\chi^2 = 16.065$, $P < 0.005$). However, two rats receiving Hartmanns's solution also had similar

TABLE I. *Neurological sequelae of 100-μl h^{-1} subarachnoid infusions. Five rats in each of the 10 groups. (Mean weights of the control group, bupivacaine group, lignocaine group and 2-chloroprocaine group were 220.8, 212.1, 208.1 and 220.9 g respectively)*

Infusion and duration	Total dose infused (mg)	Residual paralysis Yes	No
Hartmann's solution			
24 h	—	0	5
0.5% Bupivacaine			
24 h	12.0	4	1
6 h	3.0	3	2
3 h	1.5	2	3
1.5% Lignocaine			
24 h	36.0	5	0
6 h	9.0	3	2
3 h	4.5	0	5
2.0% 2-Chloroprocaine			
24 h	48.0	4	1
6 h	12.0	4	1
3 h	6.0	2	3
Totals		27	23

TABLE II. *Histological findings in 23 rats with no residual paralysis*

	Histological findings		
Infusion	Abnormal	Normal	Total
Hartmann's solution	2	3	5
0.5% Bupivacaine	1	5	6
1.5% Lignocaine	7	0	7
2.0% 2-Chloroprocaine	4	1	5
Totals	14	9	23

TABLE III. *Histological findings in 27 rats with residual paralysis*

	Histological findings		
Infusion	Abnormal	Normal	Total
Hartmann's solution	0	0	0
0.5% Bupivacaine	2	7	9
1.5% Lignocaine	6	2	8
2.0% 2-Chloroprocaine	7	3	10
Totals	15	12	27

neuronal changes. Otherwise, neurones looked healthy, with central nuclei and well stained Nissl's substance (fig. 2). No correlation could be found between these histological changes and the clinical findings.

A mild inflammatory and granulomatous reaction was present around some of the catheter sites, but in no case was this severe (fig. 3). In some animals the catheter appeared to impinge on the lateral white columns of the cord, but these animals had not shown any neurological deficit before the infusion, so that this finding could not be important. The ganglia and nerve roots appeared normal and there was no evidence of demyelination.

DISCUSSION

There has been a gradual move towards the use of continuous extradural infusion of local anaesthetics for obstetric and postoperative pain relief (Evans and Carrie, 1979; Matouskova, Hanson and Elmen, 1979; Ross, Clarke and Armitage, 1980; Davies and Fettes, 1981; Taylor, 1983). The alleged advantage is that "soaking the nerve roots in local anaesthetic might reduce the incidence of unblocked segments" (Evans and Carrie, 1979). However, the potential problem of neurotoxicity resulting from such continuous exposure in the extradural space has not been tested adequately, especially if inadvertent intrathecal infusion occurred after accidental dural puncture.

After case reports of neurological sequelae resulting from the use of 2-chloroprocaine (Ravindran et al., 1980; Reisner, Hochman and Plumer, 1980), both *in vitro* and *in vivo* studies were performed to

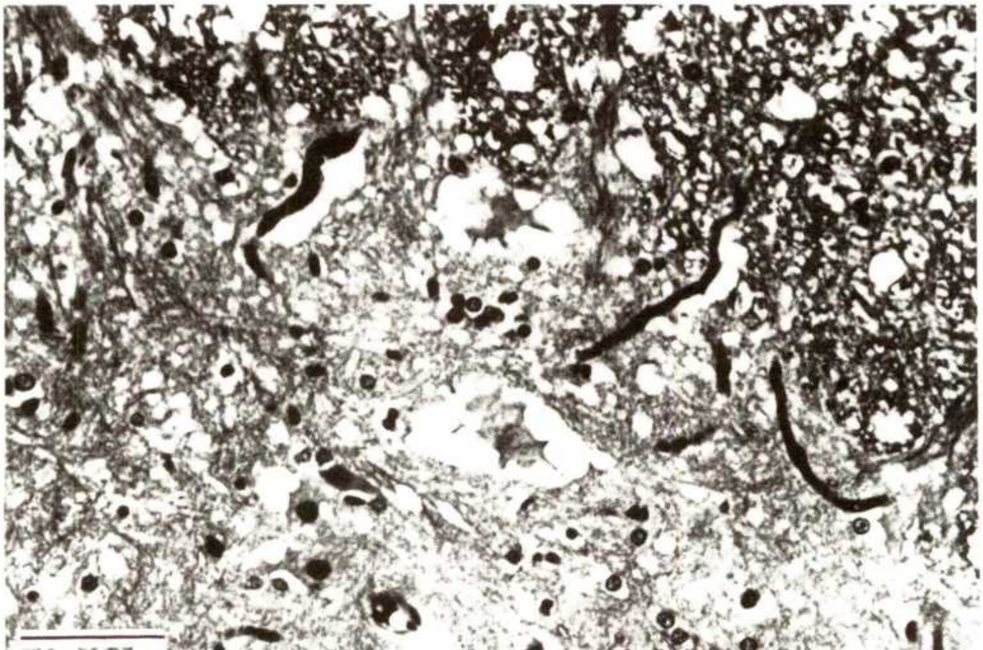

FIG. 1. Neurones of anterior horn with perineuronal and intracytoplasmic vacuoles. Kluver-Barrera stain. Horizontal bar represents 0.1 mm.

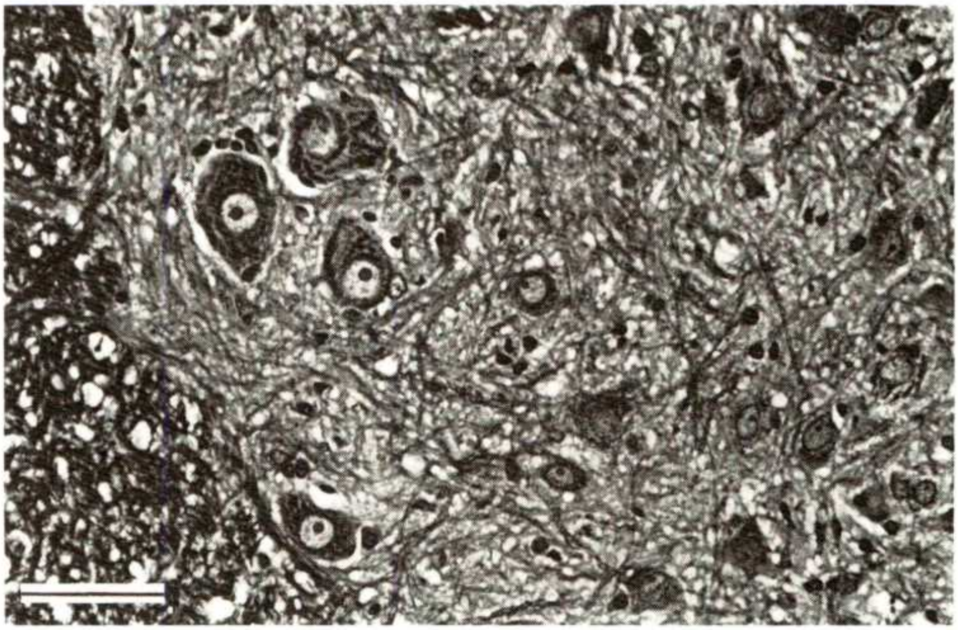

FIG. 2. Well preserved neurones of anterior horn. Kluver-Barrera stain. Horizontal bar represents 0.1 mm.

study the neurotoxicity of local anaesthetics in common use. *In vitro* studies which exposed the vagus nerve of rabbits to local anaesthetics in air showed conflicting results (Riggi, Harding and Hashim, 1981; Barsa et al., 1982), possibly because the process of oxidation of the drugs was not controlled (James, 1982). Results from *in vivo* studies were also inconclusive. 2-Chloroprocaine was more

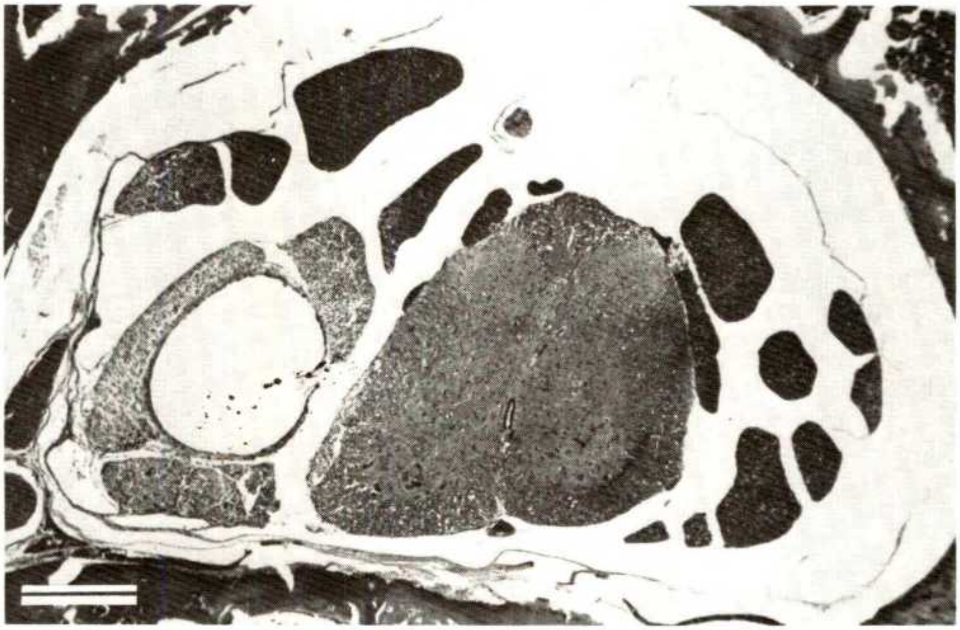

FIG. 3. Catheter site with granulomatous reaction lateral to spinal cord in the subdural space. Haematoxylin and eosin. Horizontal bar represents 5 mm.

neurotoxic in two studies (Ravindran, Turner and Muller, 1982; Wang et al., 1982), while others found no difference between the various local anaesthetics and control solutions (Feldman and Covino, 1981; Ready et al., 1983; Rosen et al., 1983). We re-examined the effects of 2-chloroprocaine and compared them with the effects of two other agents (bupivacaine and lignocaine) which had not previously been tested in this controlled way, and found all three to behave similarly.

We carried out experiments with continuous infusion intrathecally, since it was assumed that this would result in the most constant exposure to potential toxicity. Results from these experiments support this concept and show that, in unanaesthetized rats, prolonged exposure of nervous tissue to the local anaesthetics studied produced neurological deficit if the dose was large enough. The three agents were equally likely to cause such deficit, and showed a similar relationship between the duration of exposure and clinical effects: the longer the exposure, the worse were the neurological sequelae.

In most of the earlier experiments, large volumes of local anaesthetics were administered by bolus injection to the subarachnoid space of animals. This invariably caused apnoea and wide cardiovascular fluctuations in the animals, and must have affected the vascular perfusion of the spinal cord, which could have contributed to the neurological deficit found in the animals after the experiment (Kane, 1981). In our study arterial pressure was not measured because of technical difficulty in mobile, unanaesthetized animals, However, it seems reasonable to assume that arterial pressure was fairly stable, even though there was a steady block just below the thoracic region, since all the rats were eating, drinking and micturating normally during the periods of the infusions.

In the present investigation the catheter was put into the subarachnoid space 3–5 days before the infusion. This avoided repeated lumbar puncture to give intrathecal injections (Ravindran, Turner and Muller, 1982; Ready et al., 1983; Rosen et al., 1983) which could have caused traumatic injury to the spinal cord, and it allowed a period to ensure normal function after catheterization.

The pH of the solutions we studied ranged from 3.05 to 6.29, which is comparable to those used in previous studies. It has been shown that low pH (3.0), normal saline solution did not produce residual paralysis (Ravindran, Turner and Muller, 1982).

It seems likely, therefore, that the local anaesthetics *per se* were the causative factor in the observed residual paralysis, and that 2-chloroprocaine behaves just like the other agents. It would be appropriate to compare the rat with other animal models to examine the consistency of response.

There are still aspects to be clarified. It is likely, but untested so far in this model, that *extradural* infusion would require much larger doses of local anaesthetic drugs in order to cause similar neurological deficit, since the resulting intrathecal concentration will be much lower. Extradural infusion should therefore be safe in terms of neurological toxicity.

Histological findings by light microscopy must be interpreted with caution. The neuronal changes did not usually correlate with the clinical findings of residual paralysis, which is in agreement with other studies (Ravindran, Turner and Muller, 1982; Rosen et al., 1983). Apart from cytoplasmic vacuolation, the majority of neurones looked healthy and were still viable, with no evidence of chromatolysis. Such changes have also been reported in various toxic and ischaemic conditions. Using the same method of catheter implantation, similar histological changes were found in rats which received 10 small, repeated doses of cocaine, lignocaine, bupivacaine, normal saline and adrenaline over 2 days, although none of the animals showed residual neurological deficit (Bahar et al., 1984). At tissue level, the pharmacological behaviour of local anaesthetics given by bolus injection is probably very different from continuous infusions with lower concentration–time exposure.

Although the occurrence of abnormal histology was more frequent in the lignocaine and 2-chloroprocaine groups, the clinical findings of paralysis did not differ significantly between these and the bupivacaine groups. A more sensitive indicator, perhaps neurochemical or electron microscopy, will be necessary to study histopathological changes in the rat spinal cord after toxic exposures.

We therefore conclude that neurotoxicity can result from prolonged exposure to local anaesthetics and is dose related. Since 2-chloroprocaine did not give better or worse results than bupivacaine or lignocaine, its reported neurotoxicity in man may have been the result of the size of the bolus dose accidentally injected intrathecally, and such toxicity might occur with other local anaesthetics. The rat model should prove useful in screening other and new local anaesthetic agents.

ACKNOWLEDGEMENTS

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ACTIONS OF MORPHINE, PETHIDINE AND PENTAZOCINE ON THE OESTRUS AND PREGNANT RAT UTERUS *IN VITRO*

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SUMMARY

The effects of morphine, pethidine and pentazocine have been studied on the rat uterus in vitro. *Morphine caused a concentration-dependent decrease in the frequency of contraction of the oestrus uterus. In contrast, both pethidine and pentazocine enhanced the contraction rate. The pregnant uterus showed little response to morphine in the concentrations studied, whereas there was an augmented response to the stimulant actions of pethidine and pentazocine. Naloxone 1–100 ng ml^{-1} was unable to antagonize the uterine responses to the opioids, but higher concentrations of naloxone, when administered alone, slowed the frequency of the myogenic activity.*

The opioid analgesics are widely used in labour and the effect that the opioids may have on uterine contractility is of considerable interest. Studies on the action of morphine and pethidine on the uterus have produced conflicting results (Weinstock, 1971). In this preliminary study, the effects of these two opioids, and of pentazocine, on uterine activity have been examined in the rat, *in vitro*. Since the effects of the drugs may vary according to the hormonal state of the uterus, comparisons have been made between drug effects in oestrus uterus, oxytocin-stimulated oestrus uterus and 22-day pregnant uterus.

MATERIALS AND METHODS

The uteri were obtained either from 22-day pregnant rats, or from non-pregnant rats in oestrus (determined by the cornification index of the rat's vaginal smear), at which time in the cycle the spontaneous activity of the uterus is greatest. Rats were killed by a blow to the head and decapitation. Each of the two horns of the uterus was divided longitudinally to provide four preparations. These were suspended in Krebs–Henseleit solution at 37 °C under a tension of 1 g, and bubbled with 5% carbon dioxide in oxygen.

Contractions of the uterus were measured using an isometric transducer connected to either a Rikadenki pen recorder or a Grass 79c polygraph. Measurements were taken of frequency and amplitude of contractions over a 15-min period, first in the control state then with the drugs under study. Since the activity of the spontaneously contracting preparation was short lived, each muscle strip was used for one concentration of drug only. The experiments were complete within 45 min of setting up the preparation. Control preparations showed no significant deterioration within this period of time. The tissue was subsequently treated with oxytocin 200 μu. ml^{-1}. Once treated with oxytocin, the same preparation could be used for several concentrations of drug. The effect of naloxone on the response was also examined.

Significance was assessed using Student's paired *t* test on the absolute values. Results are expressed in the text as percentage change from pre-drug control because of preparation-to-preparation variability in frequency and amplitude of contraction.

Drugs

Morphine sulphate, pethidine hydrochloride and pentazocine base were used as the commercially available solutions for parenteral administration and dilutions were made with distilled water. Naloxone was used as the pure substance and was dissolved in and diluted with distilled water.

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RESULTS

Morphine caused a concentration-dependent decrease in the frequency of contraction of spontaneously active oestrus rat uterus. In contrast, both pethidine and pentazocine caused an enhancement of contraction rate. However, the results obtained had large standard errors as a result of the inherent variability of this preparation. More consistent, but qualitatively similar results were obtained in preparations treated with oxytocin (fig. 1).

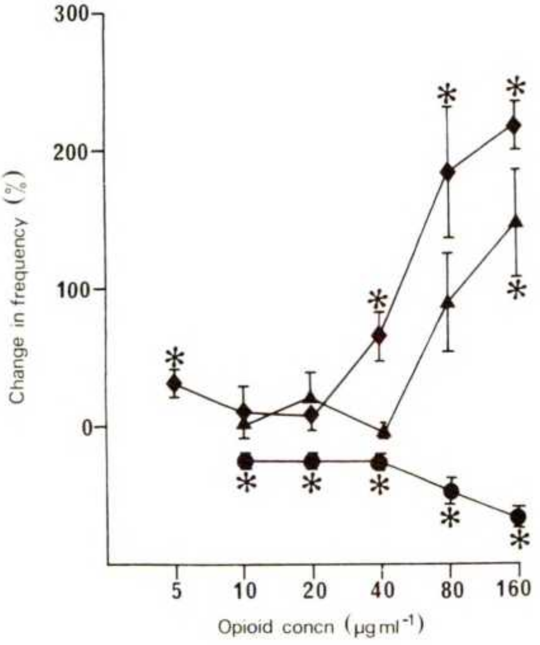

FIG. 1. Effects of morphine (●), pethidine (▲) and pentazocine (◆) on the frequency of the oxytocin 200 μu. ml⁻¹-stimulated oestrus rat uterus *in vitro*. Results are expressed as mean % change ± SEM (n = 5 or 6 preparations). *Significant change from pre-drug values ($P < 0.05$).

In general, the three opioids had little effect on the amplitude of oxytocin-stimulated contractions, except with the greatest concentrations (table I).

The frequency of the contractions of the pregnant uterus showed little response to morphine in all the concentrations used (fig. 2), but exhibited enhanced responses to the stimulant activity of both pethidine (fig. 3) and pentazocine (fig. 4).

Both pethidine and pentazocine produced very variable effects on amplitude of contractions of the pregnant uterus (table II). Some preparations showed increases of amplitude of more than 100%, and increases in resting tension were seen with the highest concentrations of pethidine and pent-

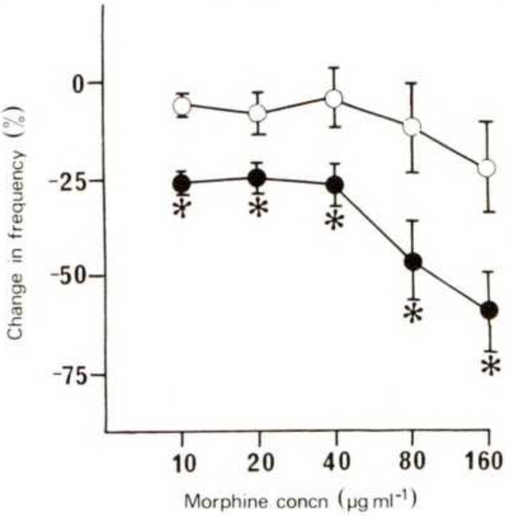

FIG. 2. Effects of morphine on the frequency of contraction of the pregnant uterus (○) and the oxytocin-stimulated oestrus uterus (●). Results are mean % change ± SEM of not less than five preparations. *Significant changes from pre-drug values ($P < 0.05$).

TABLE I. *Effects of morphine, pethidine and pentazocine on the amplitude of myogenic activity of the oestrus rat uterus, treated with oxytocin 200 μu. ml⁻¹ (mean values ± SEM)*

Concn (μg ml⁻¹)	Change in amplitude (%)					
	Morphine	n	Pethidine	n	Pentazocine	n
10	−2.0±2.0	5	+4.8±3.7	6	+7.0±3.1	6
20	−7.0+1.1	6	+5.9±2.2	5	+1.7±4.7	6
40	−2.3±2.0	6	+9.1±3.2	6	−7.0±4.8	6
80	−18.0±7.5	6	+0.3±6.3	6	−16.7±5.2	6
160	−42.4±15.3	6	−19.0±8.5	5	−29.8±8.5	6

TABLE II. *Effects of morphine, pethidine and pentazocine on the amplitude of myogenic activity of the pregnant rat uterus (mean values ± SEM)*

Concn (μg ml^{-1})	Change in amplitude (%)					
	Morphine	*n*	Pethidine	*n*	Pentazocine	*n*
10	−11.0±7.8	7	+14.7±9.8	6	+19.8±14.0	6
20	−10.6±10.4	6	+47.1±19.5	7	+50.5±18.2	6
40	+9.8±2.4	6	+96.8±44.7	7	+00.5±12.1	6
80	−1.4±11.9	6	+44.0±17.4	10	+85.3±64.3	6
160	−11.7±12.7	6	+99.0±63.8	10	+10.4±10.3	6

azocine. Morphine was without important effect on the amplitude of the contractions of the pregnant uterus.

The effects of pethidine, morphine and pentazocine on both the pregnant and non-pregnant uterus were not antagonized by naloxone in concentrations between 1 and 100 ng ml^{-1}. Greater concentrations of naloxone, administered alone, slowed the contractile frequency of the uterus; for example naloxone 1 μg ml^{-1} reduced the frequency of contraction of the oxytocin-stimulated uterus by 29 ± 7.6%.

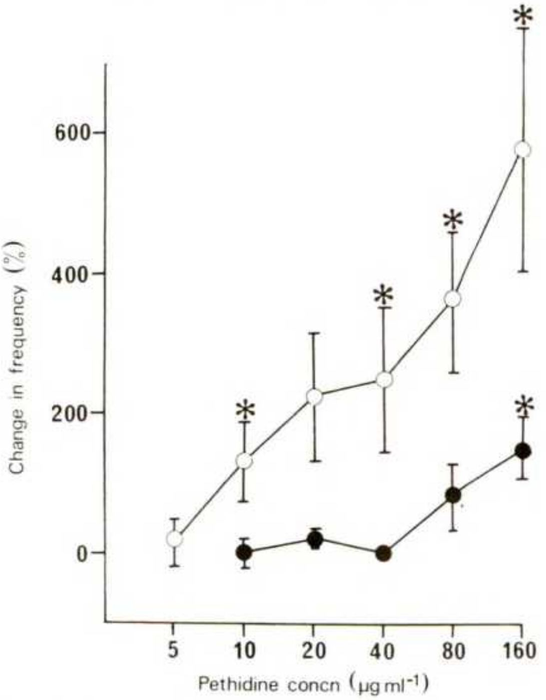

FIG. 3. Effects of pethidine on the frequency of contraction of the pregnant uterus (○) and the oxytocin-stimulated oestrus uterus (●). Results are mean % change ± SEM of not less than five preparations. *Significant changes from pre-drug values ($P < 0.05$).

DISCUSSION

In this study morphine has been shown to have negligible effects on the pregnant rat uterus *in vitro*, although significant reductions in activity were observed in non-pregnant uterine tissue. In contrast, uterine contraction rate was increased in a concentration-dependent manner by pethidine. The pregnant uterus was particularly sensitive to this effect. The response of the uterus to pentazocine was qualitatively similar to that to pethidine, except that the stimulant action of pentazocine in the pregnant tissue reached a plateau at the higher concentrations.

The action of opioids on the rat uterus is unlikely to be mediated through opioid receptors. The potency of the three drugs tested on the uterus does

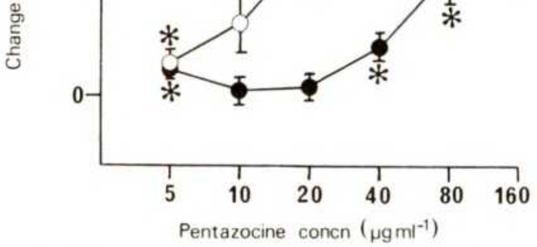

FIG. 4. Effects of pentazocine on the frequency of contraction of the pregnant uterus (○) and the oxytocin-stimulated oestrus uterus (●). Results are mean % change ± SEM of not less than five preparations. *Significant changes from pre-drug values ($P < 0.05$).

not correlate with known potencies of these agents at known opioid receptors. Furthermore, these actions could not be antagonized by naloxone.

The relevance of this study to the use of opioids during human labour is debatable, as there is considerable species variation in the response of the uterus to drugs, and relatively high concentrations of opioids were necessary to exert significant effects. Nevertheless, Campbell, Phillips and Frazer (1961) noted that women who received pethidine had shorter labours than those who received morphine, and De Voe and others (1969) observed that pethidine increased uterine force in cases of uterine inertia. A direct action of pethidine on the uterus would be consistent with these observations. Although the use of pentazocine in human labour was approved by the Central Midwives Board in 1970, little work appears to have been published on this aspect of the pharmacology of pentazocine in either man or the rat.

Further experiments are required to determine whether the isolated rat uterus is a suitable model for assessing drug activity in man.

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INVASIVE *V.* NON-INVASIVE MEASUREMENT OF ARTERIAL PRESSURE

Comparison of Two Automatic Methods and Simultaneously Measured Direct Intra-Arterial Pressure

J. VAN EGMOND, M. HASENBOS AND J. F. CRUL

SUMMARY

Two indirect arterial pressure monitors, the Finapres and the Accutorr, were investigated and compared with the direct measurement of intra-arterial pressure. Pressures in patients in a variety of circulatory states were measured and analysed in relation to two types of random error: first, the "intra-individual standard error" (within one session of measurement) and second, the "inter-individual standard error" (between sessions). (This distinction is important, since in routine monitoring of arterial pressure one is usually dealing with the first type of error only.) This study showed that sudden changes in pressure were closely followed by the Finapres. A pressure reading of the Accutorr takes about 15–20 s, meaning that, within this period, variations will not be observed. The accuracy or reproducibility of each method, as expressed in intra-individual variance, diminished in the order Intra-Arterial-Line, Finapres, Accutorr. The inter-individual variation decreased in the order Intra-Arterial-Line, Accutorr, Finapres. Most of the inter-individual variance of the Finapres is probably real because of the more peripheral position of its cuff. A correlation between malfunctioning of the Finapres and vasoconstriction or hypothermia of the finger could not be demonstrated.

Measurement of arterial pressure, either intermittently or continuously, has been used for almost 100 yr, and is now accepted practice in operating theatres and intensive care units. The direct measurement of intra-arterial pressure is used because of its accuracy, despite the additional risks. When arterial blood samples have to be taken regularly, this also calls for an invasive method of arterial pressure monitoring. However, in those patients in whom arterial samples are not required, an accurate continuous indirect arterial pressure monitor would be preferable to an invasive technique. With the advent of microprocessor-based equipment, there has been a rapid development of fully automatic indirect arterial pressure monitors. They release the clinician from the time-consuming burden of making regular (indirect) measurements of arterial pressure. However, there have been reports of damage to the ulnar and radial nerves as a result of the continuous or too frequent inflation of arm-cuffs over long periods of time (Toellner, Bechinger and Pohlandt, 1980; Sy, 1981; Schaer and Tschirren, 1982).

In our study we examined two instruments designed to avoid this disadvantage of prolonged inflation of the arm cuff. In one, the Accutorr (ACC), the period of inflation of the cuff has been shortened. The other instrument, the Finapres (FIN), uses a finger cuff rather than an upper-arm cuff. (This instrument will be commercially available through Ohio Medical Products, Madison, Wisconsin U.S.A.). Therefore, it ought to be less harmful to the patient. Moreover, it supplies a "real-time" continuous curve of arterial pressure. The aim of this study was to attain an objective judgement of the clinical applicability of both the FIN and the ACC, as compared with direct intra-arterial measurements. Simultaneous measurements with all three methods were obtained to guarantee truly comparable data. Because two methods are continuous, while the measurement of the ACC is spread over several heart beats, special precautions were made to obtain such simultaneous data.

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PATIENTS, MATERIALS AND METHODS

Patients

To provide a wide range of arterial pressure measurements, patients were selected who had to undergo major surgery or were in unstable circulatory balance in the intensive care unit. All patients required intra-arterial cannulation for reasons of the surgery or critical care itself. No selection was made for sex, age or weight of the patients, but precautions were taken to adapt the cuff size to the recommended cuff:arm circumference ratio. The patients were divided in three groups:

(1) Twenty patients undergoing major general surgery; in most instances the operations lasted several hours.
(2) Five patients undergoing open-heart surgery, studied before, during and after by pass.
(3) Seven patients treated in intensive care units.

The results of the latter two series of patients were used for judging the usefulness of the instruments in these circumstances, not to obtain information about accuracy; under these circumstances it was impossible to acquire sufficient valid data simultaneously from all three instruments. Statistical analysis has been restricted to the first series of 20 patients.

The instruments

In order to acquire comparable data for the various instruments, we performed our study by making simultaneous measurements with three instruments which are based on different principles:

Intra-arterial line (IAL). The combination of a Hewlett–Packard 78205 pressure monitor, a Statham P23 ID transducer together with a Kritoflow Catheter and a 20-gauge Teflon cannula was used. An Allen-test was performed to guarantee sufficient blood flow after insertion of the cannula in the radial artery (Husum and Berthelsen, 1981).

Accutorr. The ACC is a fully automated occlusion oscillometer (Datascope), the principle of which has been described previously (Ramsey, 1979). It detects the pressure waves in the arm cuff as a function of a continuously decreasing cuff pressure. The complete pressure decrease in the cuff during one measurement only takes 15–20 s, except in cases during which motion artefacts are detected. The apparatus is operated by a microprocessor and has a built-in printer operating in three basic modes:

(a) "Print", in which every reading (1-, 2- or 5-min intervals, or manually induced) of systolic, diastolic and mean pressures, and heart rate is printed.
(b) "Trend", in which a diagram is plotted as a trend in time; motion artefacts are also indicated.
(c) "Verify", where an amplitude diagram is drawn for each reading of the pressure-waves in the cuff as a function of cuff pressure.

Finapres. The Finapres (derived from FINger Arterial PRESsure) is an instrument developed by TNO (Utrecht, The Netherlands) and Ohio Medical Products (Madison, Wisconsin, U.S.A.) on a principle described first by Penaz (1973). It uses a finger cuff in which a photo-plethysmograph is built, measuring the absorption at a wavelength (infra-red) quite specific for arterial blood. It is fully automated by a microprocessor. It operates in two basic modes. One mode, "lock adjust", is used to verify, during one single heart beat, the plethysmograph light level for which the arterial wall is "unloaded" (transmural pressure = 0). In the other mode, in which it actually measures, a feed-back loop varies the cuff pressure around the finger to prevent the plethysmograph light level from deviating from the value determined in the "lock adjust" mode. In this mode the cuff pressure accurately reflects the pressure in the finger artery. Automatically, the instrument switches back to "lock adjust" every 20th heart beat to verify the light level to be locked on. If the instrument detects any difficulties, or has to make rather large changes in the light level, it will repeat the "lock adjust" procedure every 4th beat until stability is achieved. A session is started by an initial procedure of step-wise increases in pressure to detect the value of pressure for which the photo-plethysmograph measures maximum amplitudes and from which data the light level, for which the transmural pressure equals zero, is calculated. This level is then used during measurements as the reference for the feed-back system, until its value is updated in a "lock adjust" period.

The instrument is supplied with an alpha numerical LCD, which shows digital readings of heart rate, systolic, diastolic and mean arterial pressures, as well as error messages. Further description of the principle of this particular instrument is given by Penaz (1973) and Wesseling and colleagues (1982). Smith, Wesseling and de Wit (1983) reported on its performance.

Calibration of all transducers was performed previously in the laboratory.

Analysis of data

Most studies of arterial pressures are performed by comparing any new method of measurement with

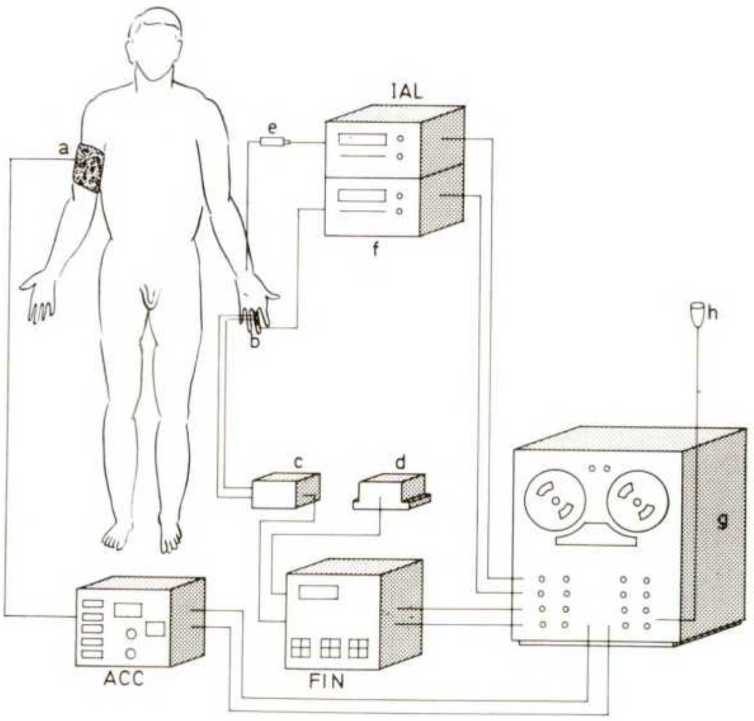

FIG. 1. Experimental procedure and description of apparatus. Arterial pressure was measured by three instruments, IAL, FIN and ACC. The output signals of all instruments were recorded on an eight-channel magnetic tape recorder (g). Two instruments, IAL and FIN, supplied analogue signals while the serial signals of ACC were recorded as well as the analogue signal of the pressure of the upper arm cuff (a). The analogue signal of the temperature monitor (f) and messages spoken into the microphone (h) were taped as well. An air pump (d) supplied the main air pressure for the FIN. This pressure was reduced to the desired value by a very fast reduction valve built in a small box (c) mounted close to the finger cuff (b). The upper arm cuff of ACC was placed on one arm; the IAL and FIN were always measured from the other arm. The resulting right–left differences will have contributed to the inter-individual variances, but would not have affected the correlation coefficients.

intra-arterial pressure, the latter being commonly accepted as the "true" arterial pressure (Bruner et al., 1981; Hutton and Prys-Roberts, 1982). However, an intra-arterial reading suffers from its own errors as a result of various factors: (1) pressure changes by flow velocity alterations* (Bernouilli's Law) or turbulence; (2) damping of the waveform by high compliance of the conducting lines (air bubbles), malpositioning of the cannula tip, or blood clotting; (3) malpositioning of the pressure transducer with respect to the level of the right atrium (the same error applies to the FIN, while for the ACC there is a comparable error in the level of the arm cuff). Furthermore, these errors are not expected to be constant over the period of monitoring during an operation; they can change as a result of movements and alteration of the vascular state. Therefore, we devised an experimental programme in which all three methods, including the IAL, were investigated simultaneously. We chose *three* simultaneous measurements because it provided the opportunity to obtain more information on the individual instruments.

Figure 1 depicts the complete experimental layout. An eight-channel Hewlett-Packard FM instrumentation taperecorder monitored continu-

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*The size of this error is commonly underestimated. Under extreme circumstances of high cardiac output and peripheral dilatation, the pulsatile flow in the radial artery may produce considerable increases (at the tip of the cannula) or decreases (along the side of the cannula) in the intra-arterial systolic pressure recorded.

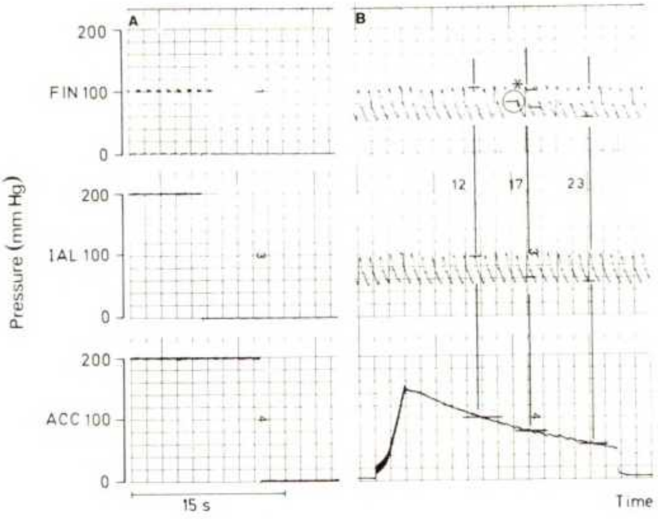

FIG. 2. Calibration and selection of simultaneous data. A: Calibration signals of 100 mm Hg for the FIN and 200 mm Hg for IAL and ACC. Zero pressure signals are supplied for all instruments. B: From the serial data of the ACC together with the analogue signal of the pressure in its cuff, the beats were selected from which systolic, mean and diastolic pressures had to be calculated in the IAL and FIN analogue pressure signals. This was achieved for systolic pressure (and similarly for diastolic and mean pressures) by selecting the beat closest to the point where the ACC cuff pressure crossed the systolic pressure value as measured by ACC and supplied in its serial signals. Note that the 16th beat (*) fell in a "Lock adjust" period of the FIN.

ously: the analogue pressure signals of the IAL, FIN cuff, ACC cuff, and a analogue temperature signal from a thermometer connected to the tip of the finger supplied with the FIN cuff. This recorder also recorded the signals from a microphone to synchronize measurements and messages on calibrations, change in the position of patient or other events, as well as serial signals (baud rate 300 BPS) of the ACC representing heart rate and the various pressure readings.

The first few minutes of each recording were used to record calibration signals for the computer corresponding to 200, 100 and 0 mm Hg. After the calibration period, the analogue signal of the pressures and other signals were recorded continuously with only brief interruptions for blood sampling and subsequent flushing or calibration. Calibration signals were automatically repeated every hour by the FIN.

Further analysis took place in four steps: data acquisition, pressure calculation, correction for level differences (if applicable) and statistical analysis.

Data acquisition. Recordings were played back to a MINC-computer (PDP 11/23 with RSX-11M operating system) with analogue-to-digital convertor, while the serial signals of the ACC were read into one of its terminal input interfaces. Three analogue signals, the cuff pressures of both FIN and ACC, and the pressure signal of the IAL were sampled with 100 Hz. Sampling started when the ACC cuff pressure increased and stopped when its pressure decreased to less than 25 mm Hg. The serial data of the ACC together with the digitized pressures were stored for later analysis in one single file.

Pressure calculation. After calibration of the three pressure signals, the computer carefully selected the heart beats closest to the crossing of the pressure readings of the ACC and its cuff pressure, and calculated the corresponding pressures for the IAL and the FIN. For instance, in figure 2 the maximum pressures of beat 12 were calculated, the means of beat 17, and the minima of beat 23 to select, carefully, simultaneous readings of equivalent pressure types with all three instruments. Precautions were made to discard noisy signals caused by diathermy and to omit those beats during which the FIN was in the "lock adjust" mode (fig. 2). The calculated data, together with the ACC readings, were stored to be analysed statistically in the next step. If corrections had to be made because of differences in the level of the transducers with respect to the right atrium, they took place at this stage.

Statistical analysis. The usual premise that the intra-arterial line measures without error was avoided. The analysis, based on linear relations between all individual methods, split the errors into two—an inter-individual as well as an intra-individual error. The reason for this is found in the internal structure of the data. The regression line in figure 3A is the regression line through the data of all patients simultaneously acquired by IAL and FIN. The two envelopes of data correspond to the data of two individual patients from these series. From this figure it is clear that the intra-individual variation is much smaller than the total variation. Therefore we made a distinction between the two types of error as indicated in figure 3B: the width of an envelope of a particular patient was determined by the intra-individual standard error (δ), and the position of the individual envelope within the envelope of all data by the inter-individual standard deviation (Δ). We assumed both types to be randomly distributed in the analysis.

The analysis was based on the assumption that all three instruments were measuring variables linearly related to the same basic value. Here the basic value might be defined as the pressure in the left ventricle. ACC measures a phenomenon related to the brachial arterial pressure in the right arm and measures a value that will be linearly related to this basic value. Naturally, the same holds for the finger arterial pressure in the left arm measured by the FIN.

At first, linear regression was performed on observations of pairs of methods, obtained in individual patients, separately for systolic, diastolic and mean pressures. Thus, we were able to obtain for each patient, and for each pressure, three correlation coefficients (CC) describing the correlation of data obtained in exactly the same circumstances at exactly the same time. By comparing, for example, first IAL and FIN and then IAL and ACC, and restricting ourselves to one measurement session (Δ is constant) we concluded, from a decreasing CC, that ACC correlates less with the desired value than does FIN. This analysis enabled us to rank the performance of the three methods for each individual patient and each individual pressure. It also allowed us to obtain an estimate of the intra-individual standard errors (δ of each method) for the particular combination of patient and instrument during a monitoring session. A high CC represented correlation and occurred only when both instruments followed the phenomena in a reproducible way (small δ). It does not prove absolute accuracy. The latter was determined (next to the regression coefficients) by both δ and Δ, the first of which, the "intra-individual" error, was obtained from the analysis of individual data. The second, Δ, or "inter-individual" error, was obtained in a similar way, taking the measurements of all patients into account. The

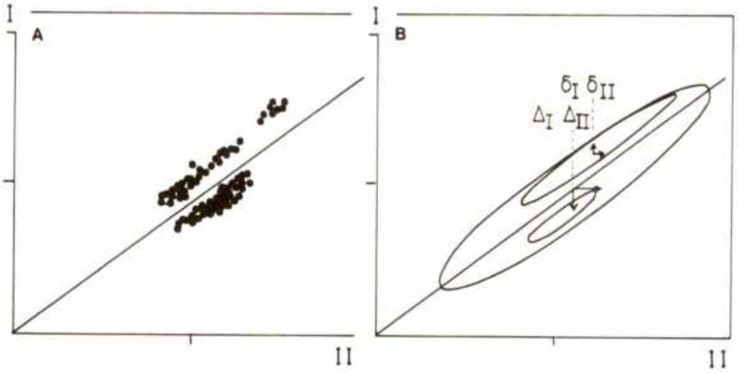

FIG. 3. Internal structure of the data. A: Actual (systolic) data of two patients as measured by FIN and IAL (division marks at 100 mm Hg). The regression line was calculated on the integral set of data obtained from 20 patients in the operating room. B: Schematic explanation of the structure in these data. All observations are scattered within a big envelope surrounding all measurements. The two smaller envelopes, surrounding the data of two individual patients, within the first, show that the intra-individual variance was much smaller than the total variance. The scatter within an individual envelope around its main axis is determined by the two intra-individual errors δ_I and δ_{II}. The scatter of individual envelopes is related to the inter-individual errors Δ_I and Δ_{II}.

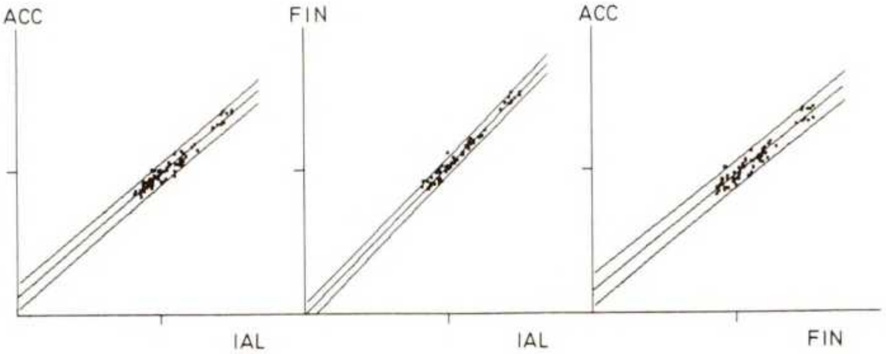

FIG. 4. Linear regression of a systolic pressure data-set. Regression analysis was performed on individual data-sets, in this case from patient No. 3 (table I). Regression lines (with 95% confidence limits) as well as measured data are depicted for pairs of instruments. From a narrowing data envelope (or from narrowing confidence limits) we concluded that the contribution of the intra-individual errors was diminishing compared with the variations of the pressure. In this case, clearly, the variance resulting from the ACC is larger than those of FIN and IAL.

mathematics of the calculation of these errors is summarized in the Appendix.

The term "intra-individual" error is used because it does not contain systematic (this is, constant within a single session) errors introduced by the particular combination of arm, cuff and transducer. For

TABLE I. *Linear regression analysis of arterial pressures. Results of linear regression on data of systolic arterial pressures (mm Hg) from five of 20 patients in the operating room. Pat. No.=Patient identification. CC=Correlation coefficient. N=Number of triplet measurements. I–F=Correlation coefficient for data of IAL and FIN; I–A=same, IAL and ACC; F–A=same, FIN and ACC. Ranks=Performance ranks according to CC. SDi=Estimation value of δ of IAL; SDf of FIN, SDa of ACC. Numbers are rounded to integer values. At the bottom of each part, ranges and averages of the integral data-set of 20 patients are listed for each instrument. * Indicates that analysis of variances only supplied upper limits (see appendix)*

						A—Systolic pressures						
				CC			Pressure ranges (mm Hg)			δ (mm Hg)		
Pat.	No.	*N*	I–F	I–A	F–A	Ranks	IAL	FIN	ACC	SDi	SDf	SDa
V	1	25	0.97	0.49	0.50	2 1 3	82–117	83–122	86–111	2	1	7
H	2	53	0.86	0.77	0.71	1 2 3	88–102	77–104	91–112	1	3	3
M	3	67	0.99	0.97	0.96	1 2 3	81–149	86–153	81–142	<3	<3	<4*
VS	4	136	0.98	0.88	0.85	1 2 3	94–157	79–142	83–121	<3	<3	<4*
H	5	75	0.89	0.36	0.37	2 1 3	75– 96	71– 87	87–103	1	1	3
all		2258					60–183	51–162	60–170			
						average	112	99	102			
						B—Diastolic pressures						
V	1	25	0.94	0.42	0.32	1 2 3	45– 61	56– 74	47– 78	<1	<1	<9*
H	2	53	0.70	0.36	0.23	1 2 3	52– 68	50– 66	48– 74	<2	<2	<6*
M	3	67	0.99	0.95	0.94	1 2 3	37– 78	33– 74	44– 92	<1	<1	<4*
VS	4	136	0.95	0.90	0.84	1 2 3	41– 68	35– 66	51– 80	<2	<2	<3*
H	5	75	0.96	0.51	0.55	2 1 3	40– 51	42– 55	48– 70	<1	<1	<5*
all		2258					37– 92	32– 95	38–103			
						average	59	54	65			
						C — Mean pressures						
V	1	25	0.97	0.60	0.59	1 2 3	55– 77	63– 88	67– 94	1	1	6
H	2	53	0.86	0.75	0.67	1 2 3	68– 84	63– 78	68– 90	1	2	3
M	3	67	0.99	0.97	0.96	1 2 3	52–106	50–101	56–106	<1	<1	<3*
VS	4	136	0.97	0.90	0.86	1 2 3	57– 93	48– 89	64– 94	<2	<2	<3*
H	5	75	0.97	0.80	0.79	1 2 3	52– 66	51– 66	62– 83	0	1	3
all		2258					50–131	43–113	46–144			
						average	78	70	80			

TABLE II. *Frequencies of performance ranks for measurements in operating room. A = Summary of the frequencies of rank numbers as calculated from data of 20 patients in the operating room. In the analysis of systolic pressures IAL scored 16 times rank 1 and 4 times rank 2. From the diagonal elements it is obvious that, for all pressure types, the order of performance of the instruments is: IAL > FIN > ACC. B = Summary of performance ranks of data in high arterial pressure range selected from measurements in the operating room. C = Summary of performance ranks of the various instruments in low pressure range. D = Summary of performance ranks calculated on data selected from patients with cold fingers in the FIN-cuff (less than 25°C), and also selected in a low pressure range (systolic less than 100 mm Hg)*

	A — Patients in operating room ($n=20$)								
Type	Systolic			Diastolic			Mean		
Meth.	1	2	3	1	2	3	1	2	3
IAL	16	4	0	15	5	0	16	4	0
FIN	4	14	2	4	11	5	3	14	3
ACC	0	2	18	1	4	15	1	2	17
	B — Data in high pressure range ($n=7$)								
IAL	6	1	0	5	2	0	6	1	0
FIN	1	4	2	2	4	1	1	6	3
ACC	0	2	5	0	1	6	0	0	7
	C — Data in low pressure range ($n=14$)								
IAL	9	5	0	8	6	0	6	8	0
FIN	5	7	2	6	5	3	7	6	1
ACC	0	2	12	0	3	11	1	0	13
	D — Data low pressure range, hypothermia ($n=8$)								
IAL	5	3	0	5	3	0	3	5	0
FIN	3	3	2	3	2	3	4	3	1
ACC	0	2	6	0	3	5	1	0	7

this session-dependent type we use the term "inter-individual" error. The inter-individual errors show up in the level-differences of the centres of gravity of the individual envelopes in figure 3.

RESULTS

Linear regression analysis

Figure 4 depicts the results of the regression analysis of the systolic data of a particular patient (No. 3 in table I). A decreasing CC is indicated by a narrowing of the envelope and confidence limits of the data.

The calculated data of the pair-wise regression analysis of the first five patients in the operating room are presented in table IA, B and C, containing all CC, the ranks (summarized in table IIA), the ranges of the pressures, and the calculated intra-individual standard error (δ). If the standard error could not be solved directly, as indicated by *, upper limits are given. In table III the resulting averages of intra-individual and inter-individual standard deviations (expectation value of Δ) are given.

High and low arterial pressure ranges

To get an impression of the behaviour of the instruments in more extreme conditions, we selected as high arterial pressure data those for which the systolic arterial pressure readings of the IAL were 135 mm Hg or greater, and analysed these separately. In this way seven of the patients studied in the operating room supplied sufficient measurements for analysis. Similarly, we selected data below 100 mm Hg systolic IAL and analysed these to judge the behaviour of the instruments at low pressures. Here, 14 patients supplied enough data for analysis.

Finger temperature, as measured on the skin of the fingertip beyond the FIN cuff, was below 25 °C in 11 patients. To test the performance of the FIN under conditions of hypothermia of the finger, we also selected data in the low pressure range for these patients.

The results of the calculated ranks in these extreme situations are summarized in table IIB, C and D.

Open heart surgery and intensive care unit

To obtain an opinion of the usefulness of these instruments under these circumstances, we studied separately some patients undergoing open-heart surgery and some in recovery rooms and intensive care units. These circumstances were such that use of the statistical analysis applied to the general surgical group was not appropriate; for most patients in this group we found it difficult to acquire enough simultaneous measurements, as a result of motion artefacts (recovery or intensive care unit), blood sampling, diathermy and perfusion (open-heart surgery).

Although an extensive presentation of data for the group of patients undergoing heart surgery and those receiving recovery room intensive care is not feasible, some interesting experiences emerge from them with regard to the FIN. In figure 5 we show an example during open heart surgery. It can be seen that very irregular patterns of pressure waves were very well followed by the FIN, even during the perfusion. After perfusion the normal patterns return in the IAL as well as in the FIN. Figure 6 shows systolic "spikes" of almost 180 mm Hg in a patient undergoing open heart surgery. It indicates that,

TABLE III. *Summary of errors and confidence limits (mm Hg). Errors (mm Hg) and confidence limits of the instruments in the various operating conditions. The meaning of the numbers in the order of the columns are: 1 = intra-individual standard error; 2 = inter-individual standard error; 3 = error from the uncorrelated action of both; 4 = confidence limits (95%) of a single beat measurement; 5 = confidence limits in "average" mode, averaging eight successive beats for FIN and five successive beats for IAL (5-s average with heart rate 60 beat min^{-1}) not applicable for ACC; 6 = confidence limits of difference of two single measurements in a session; 7 = confidence limits of difference of measurements in a session obtained in "average" mode, not applicable for ACC; 8 = average difference for all measurements in the operating room as compared with IAL. Confidence limits are calculated as ± (Student's)* t *(v, 0.05)* × √ *(variance). If numbers are not meaningful because ACC has no short term "average" mode, this is indicated with* ***

	Standard errors			95% Confidence limits				
Instr.	δ	Δ	Sum	Single	Average	Diff. single	Diff. average	Offset IAL
				Systolic pressures				
IAL	1.4	2	2.4	4.8	4.1	3.9	1.7	0
FIN	2.6	7	7.5	14.6	13.8	7.2	2.5	−13
ACC	4.1	5	6.5	12.7	***	11.4	***	−10
				Diastolic pressures				
IAL	1.4	2	2.4	4.8	4.1	3.9	1.7	0
FIN	2.8	7	7.5	14.8	13.9	7.8	2.7	−5
ACC	3.8	5	6.3	12.3	***	10.5	***	+6
				Mean pressures				
IAL	1.4	2	2.4	4.8	4.1	3.9	1.7	0
FIN	2.8	7	7.5	14.8	13.9	7.8	2.7	−8
ACC	3.8	5	6.3	12.3	***	10.5	***	+2

although in the beginning the Fin had problems adjusting the feed-back amplification to suppress oscillation, nevertheless, it was able to follow very rapid variations in pressure. In preliminary experiments we found that these oscillation problems were less severe when cuff dimensions are selected carefully to match the finger. This phenomenon will be the subject of a subsequent study.

DISCUSSION

Some basic preliminary considerations

The ACC detects pressure waves, which are small when the cuff is inflated to a pressure near the systolic or diastolic values and maximal when the cuff pressure is near the mean pressure. It detects systole when the waves appear above the noise, and diastole

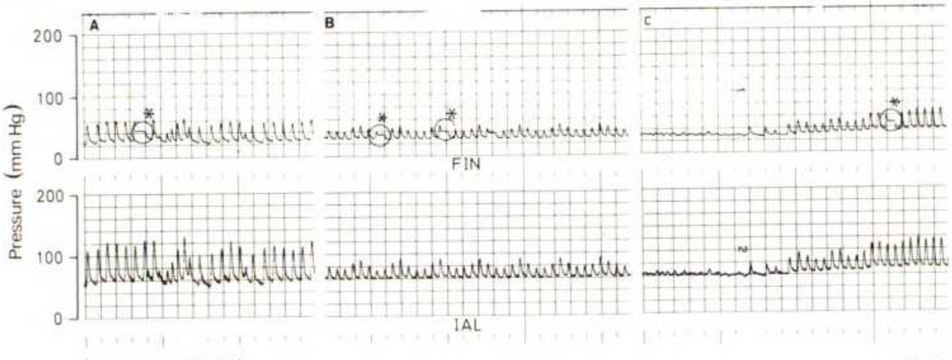

FIG. 5. FIN and IAL during open heart surgery. Example of recordings of FIN (upper trace) and IAL (lower trace) before (A), during (B) and after (C) by-pass. Note that the very irregular patterns in pressure are very well followed by FIN, with the exception of "Lock adjust" periods (*). At the end of the by-pass (C), FIN had no problem picking up the pressure waves again. The lower level at which FIN measured with respect to the IAL is obvious through this whole session.

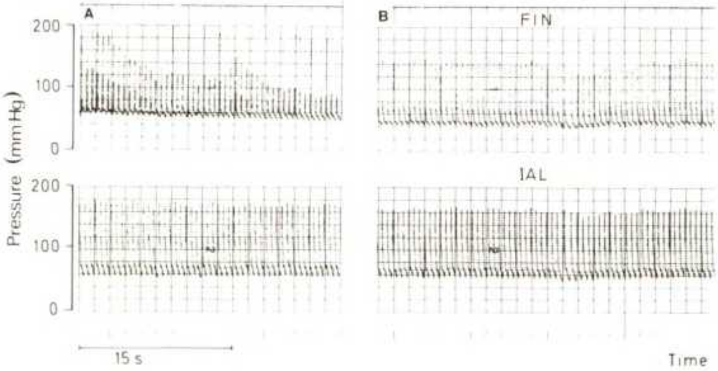

FIG. 6. Systolic spikes. Example of tracings of IAL and FIN in a patient with systolic "spikes". The left side (A) shows that FIN had at first some problems in adjusting its feed-back amplification to avoid oscillation. However, (B) shows that, after a few minutes, FIN was able to follow the fast pressure changes well.

when the waves disappear in the noise. Theoretically, therefore, ACC will provide low systolic values, especially for bad signal:noise ratios as, for instance, when the cuff is poorly positioned. For the same reason diastolic values would read too high. One expects also that the mean-pressure reading of this instrument will be more reproducible than either systolic or diastolic values.

The FIN registers the pressure in a more distal position than the IAL. Therefore all three pressures are expected to be proportionally lower.

The anaesthetist is dealing with an individual patient and requires a pressure registration that is both accurate and rapid in its response to changes in the real arterial pressure. The accuracy is determined mostly by the intra-individual variance. The absolute level at which the apparatus measures and the variation of this level from patient to patient, expressed in the inter-individual error, is less important during a single anaesthetic.

Correlation coefficients

As the correlation coefficients indicate the accuracy with which the instruments follow the variations in the real arterial pressure in comparison with the random errors superimposed on them, consideration of the regression coefficients (a and b in the equation: $y = ax + b$) becomes less important. A correlation coefficient close to 1 means that both instruments follow the variations present. An offset (b) or a proportional error (a not equal to 1) are systematic and can be taken into account or corrected for. From tables II and III we conclude that, on average, the accuracy of measuring intra-individual pressure variations is in the order: IAL > FIN > ACC.

Special attention was paid to those sessions in which ACC functioned more accurately than did the FIN. In most instances it showed that there were difficulties with the positioning of the FIN cuff, and subsequent problems in obtaining an adequate plethysmogram. In these circumstances the FIN gave messages such as "Locked on low plet" or "No plet detected". It is likely that this type of problem can be avoided by the use of a cuff the dimensions of which are more appropriate to those of the finger. We had only one cuff size available at the time of the experiements.

High and low pressure ranges, and hypothermia

As can be concluded from table IIB, the order of accuracy of detecting intra-individual variations in the high pressure range (systolic arterial pressure between 135 and 220 mm Hg) was: IAL > FIN > ACC. The same held for low pressure ranges (table IIC) and the combination of low pressure and hypothermia (table IID).

CONCLUSION

We have tested two new automatic arterial pressure monitors for accuracy and applicability in clinical situations against intra-arterial measurement. In the analysis we did not start from the (usual) premise, that the intra-arterial measurement is without error, but we calculated the various errors for all three instruments. It shows that the error of the intra-arterial measurement in most instances is very small, confirming that this method can usually be treated as the standard.

The ACC is a reasonably accurate oscillometer with two advantageous features: it is simple to use;

fully automated, with build-in printer and display; and it is safe to the patient; the inflation period has been shortened to only 15–20 s.

The FIN is an even more accurate device that can replace intra-arterial measurements in many istances. Because it is fully automated, it is simple, accurate and (for the anaesthetist) has the advantage of supplying the full analogue pressure curve, which can be displayed on an oscilloscope.

From table III it follows that the overall accuracy of the two instruments was about the same (95% confidence levels ± 15 mm Hg for FIN and ± 12.5 mm Hg for ACC), but that the FIN was more accurate in following pressure changes within a session (95% confidence limits for FIN are ± 7.5 for comparison of two individual measurements within a single session or ± 2.5 if "average" mode was selected, compared with ± mm Hg for ACC). The latter data were obtained over periods of several hours; short-term variations were followed by FIN within 1 mm Hg. However, there was a pressure decrease as compared with intra-arterial measurements, as a result of the peripheral position of the FIN cuff. The inter-individual variaiton of this pressure decrease contributes to the reported inter-individual error. Except for extreme situations (fig. 5) these differences are small.

APPENDIX

We describe a system of three different measurements A, B and C linearly related to the same "basic" quantity X (e.g. the pressure in the left ventricle):

$$A_{ni} = m_a X_{ni} + A_o + \Delta_{an} + \delta_{ai} \tag{1}$$

with similar relations for B and C.

The regression coefficients m_a and A_o are those obtained in a normal linear regression analysis, X being the independent and errorless variable. Here i indicates a measurement number; n is a patient index, while Δ is an individual offset introduced by the particular combination of patient and method while δ is the residual intra-individual random error (see also fig. 3).

The relations (1) imply mutual linear relations between A, B and C:

$$A_{ni} = m_{ab} B_{ni} + A_{bo} + \Delta_{abn} + \delta_{abi} \tag{2}$$

In (2), Δ and δ are composites of the Δ and δ in (1). The deviations from a regression line (e.g. for A and B) are therefore the result of errors in both methods and distinction can hardly be made as to which of the two is contributing most (Himmelblau, 1970). Combining the measurements of three methods makes distinction simpler.

Remaining within the data of one particular patient (n) and session (Δ is constant) we may write for the variances of X and A:

$$\mathrm{Var}(X) = S_x^2 = \frac{\Sigma(X_{ni} - \mathbf{X}_n)^2}{(N-1)} \tag{3}$$

$$\mathrm{Var}(A) = S_a^2 = \frac{\Sigma(A_{ni} - \mathbf{A}_n)^2}{(N-1)} = m_a^2 S_x^2 + \sigma_a^2 \tag{4}$$

denoting σ for the standard error of the intra-individual residuals δ. The first term at the right hand side of (4) expresses the variance resulting from the variation of X transformed by its correlation with A. The ratio of the two terms in (4) expresses the reproducibility of measurements with method A for this particular patient.

For the CC of data of this patient one finds, using the absence of correlation between variations of X and δ:

$$R_{ax}^2 = \frac{(\Sigma A_{ni} X_{ni} - \Sigma X_{ni} \Sigma A_{ni}/N)^2}{\left(\Sigma X_{ni}^2 - \dfrac{\Sigma X_{ni} \Sigma X_{ni}}{N}\right)\left(\Sigma A_{ni}^2 - \dfrac{\Sigma A_{ni} \Sigma A_{ni}}{N}\right)} = \frac{S_x^2}{S_a^2} \tag{5}$$

and, applying the fact that δ_a and δ_b are not correlated:

$$R_{ab}^2 = R_{ax}^2 R_{bx}^2 \tag{6}$$

It follows that:

$$R_{ax}^4 = R_{ab}^2 R_{ac}^2 / R_{bc}^2 \tag{7}$$

Using this solution of R_{ax} in (5), together with (4), then yields:

$$\sigma_a^2 / m_a^2 = (1 - R_{ax}^2) \frac{\Sigma(A_{ni} - \mathbf{A}_n)^2}{(N-1)} \tag{8}$$

the erroneous contribution to the variance of method A. Bold capitals stand for individual averages.

If the solution of R_{ax} is > 1, solution of (8) gives negative values for the variance. In that case one can find an upper limit for the variance, taking:

$$\begin{aligned} \sigma_a^2 / m_a^2 &\leqslant (1 - R_{ab}^2) \frac{\Sigma(A_{ni} - \mathbf{A}_n)^2}{(N-1)} \text{ and} \\ \sigma_a^2 / m_a^2 &\leqslant (1 - R_{ac}^2) \frac{\Sigma(A_{ni} - \mathbf{A}_n)^2}{(N-1)} \end{aligned} \tag{9}$$

Substituting $\boldsymbol{A}_n$ for A_{ni} and $\boldsymbol{A}$, the average of all measurements of all patients, for $\boldsymbol{A}_n$ in the formulae above results in estimates of the standard inter-individual error Δ.

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EEG CHANGES DURING CAROTID ENDARTERECTOMY: DRUG EFFECT AND EMBOLISM

B. L. GRUNDY, M. W. WEBSTER, E. T. RICHEY AND P. N. KARANJIA

SUMMARY

Clinical neurological status and the electroencephalogram (EEG) were monitored during right carotid endarterectomy under regional anaesthesia in a patient who had suffered two prior cerebral infarctions. No change in EEG or clinical status was seen with occlusion of the carotid artery, but generalized encephalopathic changes were seen after a small dose of narcotic given before carotid occlusion. Bihemispheric changes in EEG and neurological status occurred upon release of carotid occlusion. This case demonstrates three important points. First, EEG changes can be seen with sedative or anaesthetic agents in patients who have previously suffered brain injury. Second, temporary neural dysfunction may be seen remote from the site of a localized injury to the brain—a phenomenon known as diaschisis. Finally, this report reiterates the observation that the risk of injury to the brain during carotid endarterectomy is not limited to the period of possible ischaemia during occlusion of the carotid artery.

Many surgeons and anaesthetists believe that the incidence of neurological injury associated with carotid endarterectomy can be reduced by the intraoperative monitoring of cerebral function (Grundy et al., 1981; Sundt et al., 1981; Peitzman et al., 1982; Steed et al., 1982; Hargadine, 1984). We report changes in the EEG and clinical neurological function that were related, not to the occlusion of the carotid artery, but rather to the i.v. administration of narcotic and the declamping of the carotid artery following revascularization.

CASE REPORT

A 65-year-old right-handed man with diabetes mellitus, hypothyroidism and a previous left cerebrovascular accident suffered acute neurological deficits in memory, gait, speech and orientation. Computerized tomography with contrast enhancement showed patchy areas of recent infarction in the left parieto–occipital and right fronto–temporal regions. Angiography, 6 days after the acute episode, demonstrated severe narrowing of both carotid arteries and the left vertebral artery, with ulcerative plaques in the right internal carotid artery. An electroencephalogram (EEG) obtained before the acute event was moderately and diffusely abnormal, with slowing of background activity and major nonspecific slow-wave transients, but there were no asymmetries.

The new deficits cleared gradually and, 6 weeks after the acute episode, a right carotid endarterectomy was performed under regional anaesthesia. Neurological examination on the day before operation showed disorientation to date, impaired recent memory, minimal anosmia, acalculia, left–right disorientation, apraxia and absent reflexes in the upper extremities.

No premedication was given. A continuous infusion of 5% glucose in lactated Ringer's solution was given to prevent hypoglycaemia. Deep cervical plexus block was performed using 1.5% mepivacaine (Carbocaine) 25 ml. Monitoring included the electrocardiogram, intra-arterial pressure and central venous pressure. Arterial blood was sampled at intervals for measurement of glucose concentration, pH and oxygen and carbon dioxide tensions. The EEG was monitored continuously using traditional 16-channel recording as well as the

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automated methods previously described (Grundy et al., 1981). Neurological status was assessed at 5-min intervals during the procedure by asking the patient to perform a simple motor task with his left hand, recall a simple fact, and make a simple calculation. In addition, the patient was asked to count by fives for 2 min before operation, upon clamping of the carotid artery, on release of carotid occlusion and again following the operation.

The EEG recorded in the operating theatre before the procedure showed changes that had developed since the EEG obtained 2 months earlier. Four of the 16 channels recorded are shown in figure 1. Occipital background activity consisted of delta and theta waves, without alpha, in contrast to the previous alpha rhythm mixed with theta. There was definite asymmetry with more disorganization on the left side, particularly in the central–temporal region. At this time, arterial pressure was 130/78 mm Hg. With the patient breathing room air, arterial $P\mathrm{O}_2$ was 10.9 kPa, $P\mathrm{CO}_2$ 4.8 kPa and pH 7.46. During the operation, oxygen 4 litre min^{-1} was administered by nasal cannula. Heparin 5000 u. was given i.v. before occlusion of the carotid artery, and protamine 50 mg after completion of the endarterectomy.

During the initial surgical dissection, fentanyl 75 μg was given i.v. in increments. Arterial pressure and respiration remained stable, but the EEG showed a definite increase in delta components, and the occipital rhythm slowed from 6–7 Hz to 3–4 Hz (fig. 1). No clinical neurological change was appreciated at this time, and no further EEG changes were seen when the carotid was clamped. The same pattern persisted until release of carotid occlusion.

Upon release of the carotid artery after 18 min of occlusion for a technically uncomplicated endarterectomy, the patient suddenly became unresponsive. The EEG showed increased slowing in all areas, worse on the right side. Arterial pressure at this time was 174/57 mm Hg. Respiration was not disturbed. Arterial $P\mathrm{O}_2$ was 21.2 kPa, $P\mathrm{CO}_2$ 4.8 kPa and pH 7.42. The patient opened his eyes 13 min after the acute episode, but was aphasic and had a left hemiparesis that resolved gradually over several hours. Blood glucose concentration in the recovery room was 6 mmol litre^{-1}.

Neurological examination on the day after operation showed bihemisperic deterioration of function compared with preoperative status, with left–right confusion, sensory extinction on the left, and decreased memory for recent events. A computerized tomographic scan undertaken 2 days following surgery showed no acute change, and the patient returned to his preoperative status over the next few days. An EEG 4 days after operation was bilaterally and diffusely abnormal with a maximum occipital frequency of 7 Hz. The activity arising from the right hemisphere was more disorganized than that from the left, particularly in the central–parietal–temporal region. No additional ischaemic episodes occurred, and the patient's neurological status was unchanged on re-examination 3 months after the operation.

DISCUSSION

This case is of interest for three reasons. First, the EEG change seen after administration of a very small dose of fentanyl is surprising in view of current knowledge about the effects of fentanyl on normal EEG patterns. Our patient had received only fen-

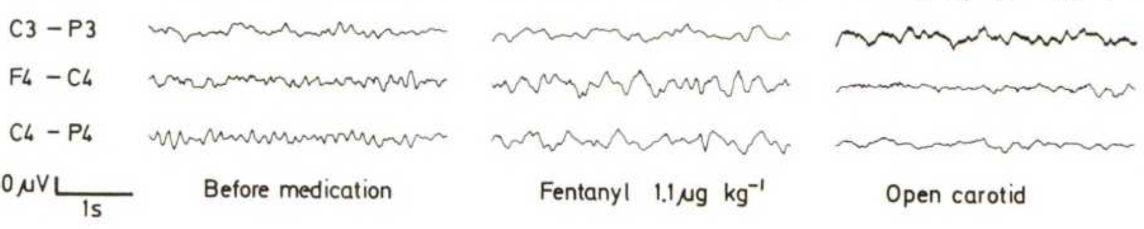

FIG. 1. Intraoperative EEG abnormalities. These segments of EEG were recorded from symmetrical bipolar channels over watershed areas of the middle cerebral artery. Odd-numberted electrode positions are on the left, even-numbered positions are on the right (Jasper, 1958). Before premedication, the activity was least abnormal on the right. A dose of fentanyl that usually produces no change on the clinical EEG was associated with slowing and delta waves of the sort seen in metabolic or toxic encephalopathy. After release of carotid occlusion, marked loss of voltage and slowing were seen on the right.

tanyl 1.1 μg kg^{-1}, without premedication—a dose that would not be expected to produce notable changes in the EEG. Kugler and colleagues (1977) found that fentanyl 2 μg kg^{-1} produced slow alpha waves mixed with theta, but delta activity was not seen. Anaesthesia with fentanyl 30–70 μg kg^{-1}, after premedication with lorazepam 4–5 mg, does not produce delta activity until moderately deep sleep has been achieved (Sebel et al., 1981). The EEG changes seen suggested exacerbation of his preoperative encephalopathy at a time when no neurological change was appreciated on the limited clinical assessment that was possible during the operation.

The second interesting aspect is the acute neurological and EEG changes that occurred with reperfusion of the carotid artery. We attributed these events to artery-to-artery embolism of either air or fibrinous material distal to the operative occlusion, even though heparin was given and the vessel was carefully flushed to eliminate air. Artery-to-artery embolism may be the main cause of stroke associated with carotid endarterectomy (Ferguson, 1982). EEG changes upon unclamping of the carotid artery have also been attributed to a steal phenomenon associated with vigorous back bleeding (Kaufman et al., 1980), but little blood loss was evident in this patient.

Finally, this patient is of interest because he had clinical signs of a new bihemispheric deficit after an apparent embolic episode to the right hemisphere. The EEG showed slowing in all cortical areas, with more dramatic abnormalities on the right. In patients who do not tolerate test occlusion of the carotid artery under regional anaesthesia, reversible signs of acute bihemispheric dysfunction are usual. These patients become unconscious within seconds, while EEG changes are still largely limited to the side of the arterial occlusion. Typically, the EEG remains asymmetrical even though bilateral changes are seen within 1 min or less.

Diaschisis, a temporary neural dysfunction remote from the site of a localized injury to the brain, has been recognized since 1914 (Von Monakow). Hemispheric blood flow contralateral to a unilateral cerebral infarction is markedly reduced for about 3 weeks after an ischaemic insult (Meyer et al., 1970). This decrease in contralateral flow is generally asymptomatic. It has been attributed to a transient depression of metabolism resulting from decreased neuronal stimulation. Loss of autoregulation, release of vasoactive substances and cerebral oedema also seem to play a role (Slater et al., 1977).

This case raises questions about the mechanisms of neurological injury during carotid endarterectomy. Only a small proportion of the neurological deficits associated with carotid endarterectomy are the result of ischaemia during carotid occlusion (Steed et al., 1982). Further examination of the perioperative events associated with neurological and EEG changes during operations performed under regional anaesthesia may help resolve the controversies that surround the methods currently used to monitor and protect the brain during carotid endarterectomy.

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ANAESTHESIA FOR CARBON DIOXIDE LASER SURGERY ON THE TRACHEA

Taking Turns in the Airway

I. D. CONACHER, M. L. PAES AND G. N. MORRITT

SUMMARY

A patient with post-tracheotomy stenosis underwent laser bronchoscopy. A total i.v. technique was used to maintain anaesthesia and provide a stable surgical field. The technique that evolved to allow the laser treatment to be carried out without impairment of ventilation or oxygenation is described.

Surgery on lesions in the trachea presents the anaesthetist with practical and logistic problems, and the advent of laser therapy has added to these. Much depends on the site of the pathology, its nature and size, and the degree of airway obstruction: anaesthetic management must be tailored to each case. In some patients it is possible to bypass the tracheal lesion using a tracheostomy and so maintain ventilation and oxygenation while the surgeon operates. Other authors have reported techniques in which anaesthetic gases have been insufflated beyond the lesion, in which venturi devices have been used or, as of late, in which generators of high frequency positive pressure ventilation have been utilized. However, with laser surgery in the upper airway, any gas conduit has to be resistant to thermal damage. The use of an adapted rigid bronchoscope allows the surgeon and the anaesthetist to share the airway and to take it in turn to operate on the lesion, and to ventilate the lungs, respectively.

CASE REPORT

Three months after tracheotomy to aid artificial ventilation following a crush injury to the chest, a 37-year-old man presented with stridor and increasing dyspnoea. Bronchoscopy revealed a ragged stricture 4 cm below the vocal cords. The diameter of the trachea varied from 0.3 to 0.5 cm at the stricture, which extended for 2 cm proximally in the trachea. It appeared to consist of fibrous tissue under the mucosa, with some tethering to distorted tracheal cartilagenous rings. Some idea of the degree of air flow restriction can be gained from the pulmonary function tests obtained on admission: $FEV_1 = 0.75$ litre (predicted value 3.70 litre); peak expiratory flow rate = 39 litre min^{-1} (predicted value 490 litre min^{-1}).

The stricture was dilated under general anaesthesia by passing a rigid, adolescent size, Negus bronchoscope through it. Although the symptoms were relieved the procedure had to be repeated on a further seven occasions in the succeeding 2 months. The possibility of using a carbon dioxide laser (CO_2 laser) was taken up, and the patient agreed to its use in the management of his tracheal stricture.

A venous cannula and a radial artery cannula were inserted under local anaesthesia in the unpremedicated patient. Anaesthesia was induced with a bolus of etomidate 20 mg, and maintained with a continuous infusion of this drug at a rate of 15 $\mu g\ kg^{-1}\ min^{-1}$. Neuromuscular blockade was produced with atracurium 50 mg and maintained, when evidence of diaphragmatic movement was seen, with incremental boluses to a total dose of 100 mg. Analgesia was produced with phenoperidine 2 mg. Arterial pressure and the electrocardiograph were displayed continuously on an oscilloscope, and samples of arterial blood were taken frequently for blood-gas analyses.

While the lesion was being assessed under general anaesthesia, ventilation was maintained through the adapted bronchoscope* with an automatic venturi device ("Injectomat" Wolf 2025). This is an electri-

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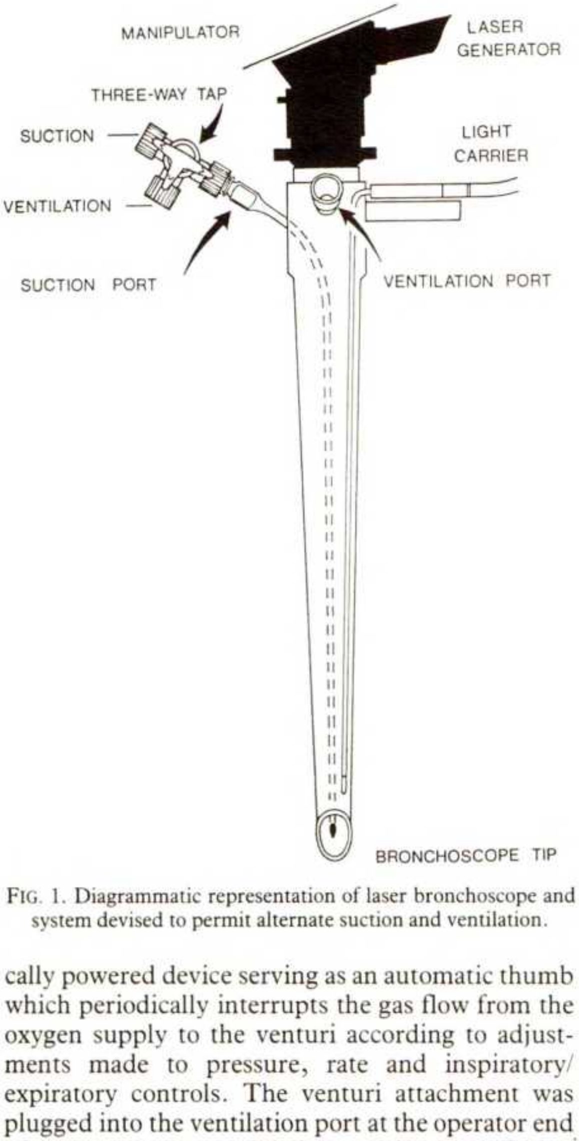

FIG. 1. Diagrammatic representation of laser bronchoscope and system devised to permit alternate suction and ventilation.

cally powered device serving as an automatic thumb which periodically interrupts the gas flow from the oxygen supply to the venturi according to adjustments made to pressure, rate and inspiratory/expiratory controls. The venturi attachment was plugged into the ventilation port at the operator end of the bronchoscope, air being entrained on inflation through the top of the bronchoscope. However, in this particular patient, two disadvantages were noted when the laser was being operated. First, there was inadequate chest movement on inflation and ventilation was impaired since the entrainment ratio was reduced severely when the main orifice was occluded by the laser manipulator (fig. 1). Second, with ventilation proceeding concomitantly with surgery, smoke particles were propelled forwards to contaminate the bronchi and distal airways.

Thus, it became necessary for the anaesthetist to take turns with the surgeon. In one phase the surgeon operated the laser with suction in progress and, in the second phase, the laser manipulator was detached from the top of the bronchoscope and ventilation carried out with the automatic venturi device. Blood-gas tensions could be maintained within an acceptable range by several variations to this sequence. Thus, the apnoeic periods during which the laser was operated were interspersed with periods of hyperventilation in a fashion reminiscent of the apnoeic oxygenation techniques described for microlaryngeal surgery: a 20–30 s laser burn phase was alternated with a period of ventilation consisting of six to eight breaths. Pa_{O_2} ranged from 12.3 kPa to 36.7 kPa and Pa_{CO_2} from 5.0 kPa to 7.8 kPa. The latter could be returned to physiological values by extending the ventilatory phase, when indicated by blood-gas results.

This evolving technique was refined further by using the bronchoscopic suction pathway, with its distally sited orifice, for ventilation also (fig. 1). A Sanders ventilation system (Sanders, 1967) was substituted for the automatic venturi device and plumbed in with a three-way tap. This enabled ventilation to be alternated with suction without having to detach the laser manipulator. The ventilation port was left open to atmosphere; this led to visible improvement in the expansion of the patient's chest on inflation as some air was entrained through the port while, on passive exhalation, it allowed the free escape of exhaled gas. Once again, arterial oxygen and carbon dioxide tensions remained acceptable.

DISCUSSION

Surgery to the upper airway requires that the anaesthetist considers the anaesthetic technique to be used, the provision of a system which will promote adequate gas exchange and, of course, the need to maintain the airway. With laser surgery these considerations must take account of the heat that is likely to be generated from the use of high energy sources on lesions in an oxygen-rich environment, and that there are products of combustion in the form of smoke and debris. No hard and fast working rules on any of these can be made, since the nature and site of lesions in the trachea or major bronchi often dictate that the approach to these problems must be flexible, and that improvisation may be necessary.

Although laser surgery in the airway is said not to be inherently painful, the presence of a rigid instru-

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*Marketed as Sharplan CO_2 Laser Bronchoscopic Delivery System, Laser Industries Ltd. U.K. Distributors: Litechnica Ltd, Adamson House, Shambles Square, Manchester M3 1RE.

ment is, and is uncomfortable and distressing for the awake patient. Moreover, any coughing or straining militates against the provison of suitable operative conditions. Thus, muscle relaxation is necessary and general anaesthesia mandatory, most clinicians electing to use a technique based on i.v. anaesthetic agents of which etomidate is a well-tried example (Versichelen, Rolly and Beerens, 1983).

At present, in the medical field, carbon dioxide lasers can only be focused along a straight line and, in the case of the upper airway, the path is supplied best by a rigid metal bronchoscope. Among the methods of maintaining ventilation with such instruments, those using the venturi devices described originally by Sanders, those using ventilating bronchoscopes (Snow et al., 1974), and those utilizing high frequency positive pressure ventilation (Vourc'h et al., 1983) have proved satisfactory.

The hazards associated with the production of heat can be decreased by the use of metal instrumentation, avoiding nitrous oxide in the anaesthetic regimen, adding nitrogen to the ventilating mixture (Vourc'h et al., 1980), and using oxygen-enriched air. In further patients treated by ourselves, incorporation of an air/oxygen mixer valve into the gas line that operates the venturi has made it possible to vary the inspired oxygen concentration, and to tailor it appropriately to keep the arterial oxygen tension within acceptable limits. This avoids higher than necessary concentrations of oxygen in the airways of patients when combustion is a possibility.

The specific needs of laser surgery in this region have meant that modifications have had to be made to rigid bronchoscopes. Vourc'h and colleagues (1983) added a welded ventilation channel that exited near the tip of the brochoscope, and the Wolf Company, through Sharplan U.K. Ltd, market a similar scope in which the narrow conduit is designed for smoke clearance. It was using this latter instrument in which the smoke clearance channel was also used for ventilation that a useful technique evolved. The technique has three phases: a ventilation sequence followed by an operative phase, and a short interim suction phase that clears the airway of some of the smoke before the next phase of ventilation which, otherwise, would push contaminated material distally. It has proved possible to automate this procedure by incorporating to the system a "black box" (M.L. Paes, personal communication) which allows easy phase alteration, and which includes a warning buzzer to inform the surgeon when suction is about to cease and ventilation start. Frequent blood-gas analyses are essential during both the manual and the automated techniques, since adjustments to the sequence of the phases may be necessary.

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PNEUMOPERICARDIUM: AN UNUSUAL COMPLICATION OF ENDOTRACHEAL LASER SURGERY

G. VOURC'H, R. LE GALL AND A. COLCHEN

SUMMARY

The case report is presented of a patient with a left upper lobe tumour of the lung in whom use of laser photocoagulation induced a pneumopericardium. The possible causes of the complication are considered.

Complications associated with laser surgery of the larynx and trachea may be caused by either the laser beam itself (fire and explosions; perforation of the thyro–cricoïd membrane or of a bronchus) or may result from barotrauma if jet ventilation is used. Fried (1984) has reviewed most of the complications seen by the laryngologist.

We report a case of pneumopericardium which complicated bronchial surgery using the neodymium yttrium aluminium garnet laser (NdYAG) under general anaesthesia.

CASE REPORT

A 60-year-old patient (59 kg; 169 cm) had been complaining of hoarseness and retrosternal pain for some months. Laryngoscopy revealed a left recurrent nerve palsy, and chest x-ray a left upper lobe tumour. The patient was admitted to another hospital. Bronchoscopy was normal; mediastinoscopy and biopsy showed enlarged, but non-malignant lymph nodes.

Two months later, the patient was readmitted. Bronchoscopy showed complete occlusion of the left main-stem bronchus; a biopsy was inconclusive, and the patient was referred for laser photoresection, and biopsy.

Bronchoscopic laser photocoagulation was undertaken. General anaesthesia, using the technique described by Vourc'h and colleagues (1980), Toty and colleagues (1981) and Vourc'h and colleagues (1983a, b), was used. Following premedication with flunitrazepam and atropine, anaesthesia was induced with flunitrazepam 0.5 mg, fentanyl 50 mg and thiopentone 400 mg, and neuromuscular blockade provided by an infusion of suxamethonium i.v. Ventilation was carried out through a rigid bronchoscope, with an M.K. 800 Acutronix jet ventilator (rate 40 b.p.m.; I/E ratio 0.2), using a mixture of 50% oxygen in nitrogen.

Resection proved impossible, since there was no plane between the tumour and the bronchial wall. A biopsy was performed, but, owing to defective forceps, some traction had to be applied on the tumour; serous fluid, which was obviously of pericardial origin, was seen to seep from the site of the biopsy.

The patient's condition, which, until this point, had been good (heart rate around 90 beat min^{-1}, systolic arterial pressure 120 mm Hg) deteriorated suddenly, with cyanosis, circulatory collapse and bradycardia, which was followed rapidly by tachycardia, auricular fibrillation and arrhythmia.

The bronchoscope was inserted to the right main bronchus, while manual jet ventilation was substituted. Auscultation of the right lung was normal, but considerable distension of the jugular vein was noted. It became apparent that there was a right pneumothorax. The bronchoscope was removed, the trachea intubated with a No. 8 cuffed tracheal tube, and a pleural drain inserted. By this time the patient was breathing spontaneously, and the ECG improved temporarily. However, this was followed by severe bradycardia and circulatory collapse. A chest x-ray showed a pneumopericardium, with tamponade (fig. 1). A transcutaneous pericardial catheter was inserted immediately with dramatic

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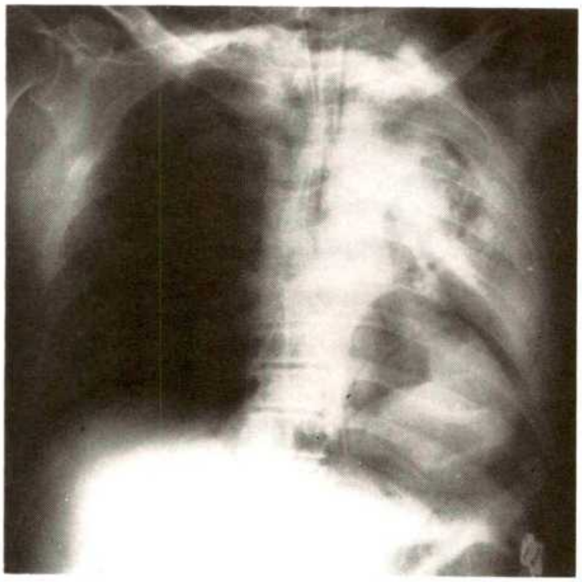

FIG. 1. Chest x-ray taken on the table, showing pneumopericardium and atelectasis of the left lung.

improvement in the patient's condition. At no time was there complete circulatory arrest, and the pupils were never dilated. An arterial blood sample (following injection of 1.4% bicarbonate solution 250 ml i.v.), was normal: Pa_{CO_2} 22.9 kPa, pH 7.37, Pa_{CO_2} 4.72 kPa. Surgical drainage of the pericardium was undertaken. The postoperative course was uneventful, the patient leaving the recovery area the following day, to be discharged 2 days later. The biopsy showed epidermoid carcinoma.

DISCUSSION

In a series of over 1000 patients, and 1200 sessions using the NdYAG laser, this is the first complication of this type that we have met. Ventilation under pressure undoubtedly inflated the pericardial cavity, and was responsible for the tamponade. The (moderate) right pneumothorax may have been induced by gases escaping into the mediastinum, and then into the pleural cavity through the bronchial tree, or by excessive pressure when the broncho was inserted to the right main bronchus.

This case report shows that laser photocoagulation, with or without biopsy, may endanger the tracheal or bronchial tree, and induce severe complications. Both surgery and anaesthesia may be involved—as was the case on this occasion. However, it is questionable whether, had the procedure been performed under topical anaesthesia as advocated by Dumon and colleagues (1982) the accident would have been avoided. Undoubtedly, the injection of gases under pressure made the pneumopericardium worse. However, the advantages provided by general anaesthesia, for the surgeon, weigh heavily in its favour.

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BOOK REVIEWS

Neural Mechanisms of Pain. Advances in Pain Research and Therapy: Vol. 6. Edited by L. Kruger and J. C. Liebeskind. Published by Raven Press, New York. Pp.364; indexed; illustrated. Price $61.00.

This volume contains the presentations made at the 16th Annual Symposium of the Intra-Science Research Foundation held in Santa-Monica, February, 1983. The subjects covered come under the general heading of "Neural Mechanisms of Pain" and present the state of the art as it was some 2 years ago. It is of great interest, therefore, to see which particular areas have developed since that time and which observations are by now obsolete. The authors of the 22 chapters are well known, not only in their own specialized loci of research, but also in the wider milieu of pain investigation and evaluation, each having made previous significant contributions to the understanding of the "highways and byeways" of nociception. It should be appreciated from the outset that this is not a book for the anaesthetic population as a whole, other than for the occasional browse or for the two chapters which are mandatory for all those concerned with analgesia. It will, however, prove of great interest and a source of discussion to those involved with the basic scientific investigation and elucidation of pain in all its aspects, and to the clinician intimately concerned with the management of chronic pain.

Obviously, some chapters will have greater appeal and clinical significance than others for the practising anaesthetist, but the papers dealing with "Multiple Spinal Opiate Receptor Systems in Analgesia" by Tony Yaksh and "Mechanisms in Acute and Chronic Pain" by Patrick Wall should be essential reading for anyone in the biological area.

At the other end of the spectrum, there will be only limited interest generated by the two chapters dealing entirely with animal work. Alas, the paper which disappoints the most is by Ronald Melzack on "Neuropsychological Basis of Pain Measurement", its data being somewhat superficial and lacking in contemporary aspects.

Nevertheless, this book should join its predecessors in the *Series* on the shelves of all Anaesthetic Department and Medical School libraries, for rarely is so much relevant and important contemporary information and opinion brought together between the covers of a single book. This volume will be a standard reference for a number of years to come and, as such, is a "Best Buy" whatever the published price.

K. Budd

Pulmonary Surfactant System. Edited by E. V. Cosmi and E. M. Scarpelli. Published by Elsevier. Pp.401; indexed; illustrated. Price $88.50.

This book consists of the invited papers presented at a Symposium on surfactant held in Rome in 1983 under the auspices of the Giovanni Lorenzini Foundation. The manuscripts have been collected and are presented in typescript form. Consequently, the book varies in legibility, and has probably been difficult to edit to any extent; it is often quite heavy going, and has frequent spelling and grammatical errors. As with most Symposia, the quality of the contributions is not uniformly high and, of course, they have not been subject to peer review or revision. Nevertheless, the contributions show how far the topic of lung surfactant has come in its short history, and emphasize its importance in lung physiology and disease. They also expose several of the misconceptions that have become enshrined in the more popular textbooks (anaesthetic textbooks included). Scarpelli's account of the contribution of surface forces to lung mechanics, and Hill's well-argued contribution on fluid forces are partly contradictory, but more plausible alternatives than the accepted concepts of surfactant action. These contributions represent balanced and well-argued re-statements of previous work and opinion and are going to be good value for the reader who picks up this book to find out about surfactant. However, they might have been thought "old hat" by a participant at the Symposium who attended to give, and listen to, papers on new work that could finally prove to be of transient or limited value. Unfortunately, these latter papers predominate. The two approaches cannot be easily reconciled. The ideal would be an overview, plus a critical reassembly of the separate contributions that might be possible after attending the Symposium. The contributions to this book were written before the meeting (which must have been very stimulating), but what is needed is what the authors thought *after* the opportunity to exchange ideas. This type of educational, rather than scientific communication, is often found in editorials or short reviews. In fact, Hill's article resembles editorials in other journals.

The book covers the fields of surfactant function and composition, neonatal and adult respiratory distress, and alveolar and bronchial clearance. Several of the papers mention ambroxol, which seems to stimulate surfactant synthesis and may be useful in therapy of RDS. A "reader friendly" version of the book would be worth buying, but in its present form the book is one for reference only.

G. B. Drummond

Future Anesthesia Delivery Systems. Edited by B. R. Brown jr. Published by F. A. Davis Company, Philadelphia. Pp.254; illustrated; indexed. Price $40.00.

The familiar anaesthetic machine has changed its shape but little in the past 50 years. Continuous flow machines of today have better flow meters and vaporizers than their predecessors, may contain one or two built-in safety features and are usually cluttered with add-on monitoring devices. They perform essentially the same basic functions as those of yesteryear in the same general way, and with the same general drawbacks. This book examines the possible influence of technological advance (and especially the impact of the microprocessor) on the future design of anaesthetic machines. The various contributors come from the disciplines of anaesthesia and biomedical engineering. They consider what we have at present and what is wrong with it, what we need and how to get it, and how close we are to achieving the "space-age" machine.

Given that the current generation of anaesthetic machines are far from perfect, an important first task in planning for the future is to define our needs. Disparate views on this are presented in this book. In general, a more sober and more realistic approach is taken by the biomedical engineering contributors than by the anaesthetists. The engineers emphasize our great lack of understanding of normal physiological control mechanisms and the compounding of this problem by anaesthesia. They contrast the comparative simplicity of applying control theory to anaesthetic equipment with the great difficulty of controlling patient variables. Advanced technology will not remove from the anaesthetist the role of a decision taker. Improved methods of measurement and data processing will assist him by presenting information in an easily assimilated form. The microprocessor will also act as an automatic pilot or "cruise control"—the anaesthetist decides what to do, the machinery ensures that it is done. With our present body of knowledge, this is a better approach to the application of advanced technology than, for instance, the description given by one group of authors of fully automated closed-circuit anaesthesia. In their technique they have "closed the loop", but because in so doing they have used a large number of greatly simplified or empirical assumptions, their approach cannot improve our understanding of the problems or lead to better solutions. Even if their method appears to work, it takes us down a blind alley. The essential difference in approach between the clinical contributors and the technologists seems to this reviewer to be that the clinician tends to decide what it would be nice to do and assumes that technology must have a way of doing it. The technologist, however, says that before providing an answer he needs from the anaesthetist a far more detailed description of the problem. Any inherent imprecision in this description will of necessity constrain the efficiency of the solution.

This book is not all about computers. There is a useful chapter by Rendell-Baker on the development of international standards for anaesthetic equipment, a discussion on how waste anaesthetic gases could be recycled, and several descriptions of newer methods available for gas flow measurement and control and for gas analysis. Possibly the most interesting chapter is the last one, entitled "What do we do until the future gets here". The message seems to be to put up with what you have—it works very well most of the time, there is little better available at present, and the sophisticated advances heralded in this book are probably a very long way off.

C. M. Conway

The Origins of Anaesthesia. By Sherwin B. Nuland. The Classics of Medicine Library. Published by Leslie B. Adams jr. Pp.131; indexed; illustrated. Price $39.00.

The aim of this beautifully produced volume is to relate the events leading up to October 16, 1846, when William Thomas Green Morton demonstrated the effectiveness of ether at the Massachusetts General Hospital. In order to review the variouis contributions the author has chosen to reproduce, in facsimile form, the various source articles of the time and, in addition, rounds off this dramatic presentation by recounting James Young Simpson's introduction of chloroform. Four key facsimile papers are reproduced which establish beyond doubt the basis of what led to modern anaesthesia. The author has brought under one cover, however, much more that is pertinent to the story of the beginnings of anaesthesia, ranging from pain relief in the Middle Ages to Mesmerism. All combine to form a gripping and, at times, tragic account of the origins of our specialty.

Many would claim, with some justification, that the greater part of the torrent of contemporary anaesthetic literature suffers from an ordinariness of presentation and lack of literary style only partially redeemed by its scientific value. Certainly, much of it is unlikely to be read 100 years from now with such enjoyment and intellectual stimulation as that provided by these few original papers of the last century. This in itself, if true, would be justification enough for the present publication.

There is, however, another compelling reason to commend Dr Nuland's effort of compilation and commentary on the origins of anaesthesia. It is rare indeed for postgraduate trainees in anaesthesia nowadays to have more than a sketchy and inaccurate knowledge of their forebears and their labours. Some even give the impression that nothing of great relevance to their current practice happened in the pre-thiopentone age. The importance of knowing where we have been, as a guide to onward direction, seems to elude many. Even a cursory dip in this volume might just disabuse them of this mistaken view and enrich their appreciation forever of the specialty which claims their allegiance. The reviewer certainly hopes so; otherwise this splendid book will be condemned to the shelves and coffee tables of a few medical history buffs and not be, as it deserves, a well-thumbed and much appreciated account, in every teaching department which still has a library budget, of possibly the most dramatic milestone in modern medicine.

D. Campbell

Acute Cardiovascular Management: Anaesthesia and Intensive Care. By A. K. Ream and R. P. Fogdall. Published by J. P. Lippincott Co. Pp. 940; indexed; illustrated. Price £62.00.

The reader should not be misled by the title, into believing this book covers all aspects of cardiovascular management in intensive care. It does, however, deal comprehensively with the perioperative management of patients presenting for cardiac and vascular surgery.

While it is a multi-author text, there appeared an overall consistency in the section dealing with clinical practice, reflecting perhaps the predominance of Stanford-based clinicians.

For the purposes of review, the book can be divided into three sections. The first deals with physiology, pharmacology and monitoring, including a chapter on the assessment of cardiac catheterization data which would be read with benefit by anyone practising cardiac anaesthesia.

The section on pharmacology was somewhat dated, as there was no discussion of calcium antagonists and the section on the cardiovascular effects of non-depolarizing neuromuscular blocking drugs seemed somewhat redundant on account of the cardiostability available with the current generation of blockers.

The second section deals with clinical practice involving perioperative management of adult and paediatric cardiac surgery. The chapter on postoperative care of the adult cardiac patient was comprehensive and that on transplantation was also of interest, in view of the authors' considerable experience in this area.

The more conservative cardiac anaesthetist would be encouraged by the fairly stringent criteria suggested for selection of patients suitable for pulmonary artery catheterization.

The section is completed by chapters on anaesthesia for major vascular surgery. Description of anaesthesia for thoracic aneurysm surgery was much appreciated by a reviewer with little experience of this area.

The last section deals with miscellaneous topics, including coagulation, hypothermia and cardiac assist devices. The section is completed by a description of training in cardiac anaesthesia as practised at Stanford. I noticed with interest that the authors place their own text at the top of the reading list and in this reviewer's opinion, they may not be far wrong.

J. C. Howie

Pediatric Anesthesia, Vols I and II. Edited by George A. Gregory. Published (1983) by Churchill Livingstone, London and Edinburgh. Pp. 1020; indexed.

These two volumes of paediatric anaesthesia are edited by Professor George Gregory from the Department of Anesthesia, University of California, San Francisco School of Medicine, California U.S.A., who has invited 23 distinguished paediatricians and paediatric anaesthetists from the United States and Canada to contribute "their talents and clinical experience". The first volume of 550 pages is principally concerned with establishing basic embryological, physiological and anatomical principles upon which the techniques of paediatric anaesthesia are described in the second volume. The editor in the preface makes the valid point that, in recent years, a great deal of much valued information concerning physiological, pharmacological and pathological variables in infants and children has become available. However, because this knowledge is reported in paediatric, anaesthetic and surgical journals and textbooks, there is a need to collate this important information where it can be more readily found, "especially in the middle of the night"! Whilst there is no doubt that paediatric anaesthesia is now widely recognized as a valid subspecialty of anaesthetic practice, such an ideal is only to be applauded, and undoubtedly Professor Gregory has succeeded admirably. It is to be hoped that the busy practitioner and house officer will be consulting these texts, not in search of guidance on how to handle the particular clinical situation, but in how to present a coherent and informed report to the paediatric anaesthetic specialist. The differences between adults, and infants and children, are rightly continually being stressed. No-one who has read the chapters should be under any illusion that the response of the young patient compared with the adult to, for example, fluid requirements, drug dose, temperature regulation, cardiovascular and respiratory effects are modified considerably; these changes are well documented.

Despite the recent increase in our knowledge of the effects of anaesthesia in infants and children, there is still a great deal of information to be obtained. It is to be hoped that some of the current concepts based on quoted adult or experiemental work will soon be replaced or modified by the results from paediatric research.

The editor made a particular plea to his contributors to stress, among other items, aspects of physiology and embryology. The enthusiasm with which they have responded to this request has inevitably resulted in some imbalance and it could be asked whether more than 60 pages should be devoted to the renal system, whilst less than 20 pages cover the cardiovascular physiology and less than 30 pages the respiratory system. Similarly, while developmental metabolism and nutrition, and temperature regulation are most important aspects of the overall care of infants and children and the information presented is fascinating, the anaesthetic resident will need many hours of the midnight oil to absorb the 145 pages devoted to these subjects. There is no doubt, however, that the academician and the specialist paediatric anaesthetist will revel in this mine of invaluable paediatric physiology. The accent certainly is aimed more at the medical approach to these problems and surgical aspects are not highlighted. How, for example, do the infant and child differ in respect of their metabolic response to surgery compared with the adult?

The second volume will have great appeal to all practising paediatric anaesthetists and covers such topics as anaesthesia for the premature infant, which is currently much in vogue because of the achievements of neonatologists in improving the survival of extremely preterm infants, anaesthesia for congenital heart disease, thoracic surgery, neurosurgical procedures and all the other specialized branches of paediatric surgery.

The final chapter deals excellently with paediatric intensive care and is accompanied by a list of 800 references. Paediatric practice in the U.K. appears to be very different in two aspects if one is to believe that "botulism is a relatively frequent cause of respiratory failure in infants". Fortunately also, thyrotoxic crisis has yet to be encountered in most paediatric intensive care units.

A great deal of hard work by all the contributors, the editor and the publisher, has made these volumes easily readable and the clear print and good diagrams make them readily understandable. Inevitably, statements are made that do not have substantiation or which cannot be agreed. Thus, on p.598 it is stated that "nitrous oxide is not without cardiovascular effects in preterm infants, decreases arterial pressure and can cause cardiac arrest". It would be interesting to know the basis on which this statement is made. Some paediatric anaesthetists will certainly question the advice that "it is usually not necessary to protect the airway with an endotracheal tube" for lacrimal sac washout, despite the assertion that the volume of fluid is very small. Doubts will also be expressed about the statement that "controlled ventilation results in rapid alveolarisation of the dye during bronchography". There are, incidentally, some minor typographical errors (Rees not Reece!), mislabelling of figure 11-13, and minor irritating colloquialisms, but on the whole the standard of proof reading is high. These small errors should not, however, be taken as any serious criticism on what is, and will remain for some time to come, a highly recommended textbook of paediatric anaesthesia. The major criticism will come from the resident anaesthetist who will find the price precludes these books from his library shelf.

Gordon H. Bush

Manual of Preoperative and Postoperative Care. By Dudrick, Baue, Eiseman, MacLean, Rowe and Sheldon. Published by W. B. Saunders. Pp. 82; indexed. Price £27.25.

This is the third edition of the *Manual of Preoperative and Postoperative Care* prepared by the Committee on Pre- and Postoperative Care of the American College of Surgeons. It is divided into four sections, covering basic problems in surgery, paediatric surgery, problems related to specific organ systems, and those relating to special categories of patients. It differs from the previous edition in that it reflects the evolving interests that have occurred in surgery within the past decade. The chapter on surgical nutrition has been expanded to include both enteral and parenteral nutrition, while the chapter on paediatric surgery has been expanded to four chapters dealing with the specific problems of paediatric surgical patients. Further chapters on preparation before operation, multi-systems failure and the problems relating to specific types of patient, for instance the cancer patient, have been added. The purpose of the manual is to provide guidelines for the pre- and postoperative management of patients undergoing both elective and emergency surgery. Technical details of operations have not been included.

Although compact, running to just over 800 pages, the manual readily achieves these aims. It is packed with good practical common-sense, albeit with a transatlantic flavour. By its nature it tends to be, in parts, somewhat didactic. Nevertheless, the advantages are that no patient should come to grief if the principles outlined are adhered to. Perhaps, in a British presentation, more attention would have been paid to the role of fat emulsions in parenteral nutrition and the value of metronidazole in antibiotic prophylaxis. There was little discussion of the management of pain after operation, and respiratory assessment before operation appeared somewhat superficial. It lacked a chapter on antibiotic prophylaxis, although this was covered to some extent in other chapters, and would have benefited from a chapter devoted specifically to the problems of management of patients with residual sepsis. It tended to be biased towards elective surgery. Naturally, the references tended to be biased towards the American literature.

These criticisms however, are minor. Overall, the book provides an invaluable guide to all those involved in the pre- or postoperative management of surgical patients. It should be of particular benefit to all Registrars in surgery, and should be obligatory reading before the Fellowship. It would also be useful for Anaesthetists who wish a global view of the management of surgical patients.

C. G. McArdle

Trauma and the Anaesthetist. By J. C. Stoddart. Published (1984) by Baillière Tindall. Pp. 189; illustrated; indexed. Price £11.95.

This book aims to provide a practical guide to the management of the injured patient for anaesthetists at all stages of their careers. It covers transportation of injured patients, priorities in care, shock, the upper airway, hypothermia and drowning, coma and head trauma, burns and a variety of insults to the respiratory system. Dr L. J. Dunkin contributes on Severe Burn Injuries and N. E. F. Cartlidge contributes on Coma and Disorders of Consciousness after Trauma. These are both valuable contributions to the book. A large percentage of the book is devoted to injury and insult to the respiratory system and reflects the author's major interest in intensive therapy.

The preliminary chapter on Priorities in the Care of the Injured Patient is very good, although the use of Entonox is dismissed somewhat summarily. The chapter on Shock is very helpful, although factors which lead to an increase in antidiuretic hormone secretion are not discussed. Whilst serum osmolality is cited as a factor concerned with ADH secretion, effective blood volume does not get a mention. I could not agree more, however, with the value of urine osmolality measurements in recognition of early acute renal failure. There is considerable discussion of septic shock which, although often a consequence of serious injury may, not be considered by everyone to fall strictly into the context of Trauma and the Anaesthetist. The section on volume replacement would benefit from a number of tables. The Table 4 referred to in the text seems to have disappeared from the chapter without trace. Much of the recommendations for management of shock are dogmatic, although this is not necessarily a bad thing in a text of this nature.

The chapter on Trauma and the Upper Airway discusses awake intubation without giving any real indications for its use. In the discussion of management of chest injuries the indications for tracheotomy are discussed before those for intubation. In the light of present day practice this does not seem entirely logical.

An inaccuracy appears in discussion of prothrombin time. During the development of adult respiratory distress syndrome the prothrombin time is described as having decreased to 50% of normal. This clearly is not the case, since the prothrombin time in these circumstances is prolonged. This misleading statement appears on no less than three occasions in this chapter. On the subject of the adult respiratory distress syndrome, the section on selection of infusion fluids might with benefit have been divided into those required in the early phase of resuscitation and those more appropriate to a later period in development of this syndrome where the phenomenon of capillary leak has become established. Much sound advice is given in the chapter on Coma and Disorders of Consciousness after Trauma, although the dose of mannitol (1.5–2 g/kg body weight) is rather high compared with that used in other specialist centres dealing with head injury.

The author is clearly a perfectionist. We are entreated to ensure perfect or immaculate fluid balance charts. Of course, this should be the case. Unfortunately, in practical terms it is very difficult to achieve. Throughout the book a commendably cautious attitude is demonstrated towards correction of metabolic acidosis. The chapter on transportation of the injured patient is particularly helpful to anaesthetists of all grades.

In summary, this is an excellent book which will undoubtedly find its way into emergency areas as well as libraries. All anaesthetists in training would do well to have a personal copy, which will not only be of great assistance for the examinaiton, but also of great help in emergency management of the trauma victim.

S. M. Willatts

Anatomy for Anaesthetists, 4th edition. Published by Blackwell Scientific Publications, Oxford. Pp.376; illustrated; indexed. Price £18.50.

The first edition of this book appeared in 1963 and immediately established itself as the standard textbook on its subject—a position which the three subsequent editions have unquestionably maintained. Professor Ellis was joined for the 3rd edition by Dr S. Feldman in order to provide anaesthetic expertise on specialist applied anatomy, although the authors still make it abundantly clear in their introduction that they have not designed a text book on local and regional anaesthetic techniques. However, the application of anatomical knowledge to the performance of nerve blocks and i.v. cannulation is a keynote of this work.

The revisions in this new edition compared with the 3rd are not extensive. The sections on arterial and venous cannulation have been rewritten. The whole text has been carefully revised and five new figures incorporated. The book was always a model of clarity, both in text and illustrations, but somehow both seem to be even clearer in this new edition. It is difficult to see how this book can be improved and it will certainly continue to fill the need of both trainees and trained for a definitive text to which they can turn, whether it be for purposes of preparing for an examination or for undertaking any procedure for which a knowledge of the relevant anatomy is essential.

P. W. Thompson

An Introduction to Neurosurgery. By B. Jennett and S. Galbraith. Published by Wm Heinemann Medical Books Ltd, London. Pp. 360; indexed; illustrated. Price £17.00.

This book, according to the cover, is directed at specialists in fields other than neurosurgery who need to know something of the subject, and neurosurgical trainees and nurses are particularly mentioned, although anaesthetists are not. The reviewer is not able to comment on the needs of trainee neurosurgeons, but the level of discussion in the book makes it suitable for only the most senior of neurosurgical nurses. It is a useful text for anaesthetists whose work involves neurosurgery; for example the classification of types of intracranial tumour and the description of prognosis and operating difficulty of aneurysms at various sites are helpful.

The discussion of intracranial pressure and its problems is adequate for the anaesthetic trainee and has the advantage over some anaesthetic texts that it includes the clinical features of increased intracranial pressure. The section on localizing clinical signs provides a useful revision of the neurophysiology and neuroanatomy underlying interpretation of such signs. The chapter on head injury provides a good overview of the problem, but the account of intensive care of severe head injury is not sufficiently detailed for the anaesthetic trainee. There is, for example, no mention of the cerebral function monitor or of evoked potentials, nor of the need for plasma phenytoin concentrations in the management of post-traumatic epilepsy.

There are quite a few type-setting errors and some misleading mistakes, for example on p.232, under "Hyperventilation", hypercapnia is said to induce severe vasoconstriction, and there is a lack of consistency in the use of non-proprietary and proprietary names for drugs.

Despite these quibbles, at £17.00 the book represents good value for the anaesthetist who wants to have an informed understanding of the clinical problems of the patients he will meet when working in neurosurgical anaesthesia.

(the late) *D. Gordon McDowall*

Clinics in Anaesthesiology, January 1984; Vol. 2 No. 1: *Intravenous Anaesthesiology*. Edited by J. Sear. Published by W. B. Saunders & Co. Pp. 266; indexed. Price £12.50.

From the title of this multi-author book, one might expect a slant towards American anaesthetic practice. However, most of the contributors are British, with authors from the U.S.A., Canada and Australia. The book is divided into two parts, eight chapters on the Clinical Pharmacology and Practice of Intravenous Anaesthesia and five chapters on Applied Pharmacology. There is a certain amount of confusion in terminology used throughout the book. There are intravenous anaesthetics, there are hypnotic agents, which appear to be benzodiazepines and non-barbiturates, and narcotics, which are in fact opioid analgesics. There is also some duplication in the chapters, telling us at least three times that Althesin is a mixture of two steroids and even more times that di-isopropylphenol is either being reformulated in a lipid emulsion or that there is a need to reformulate it (depending on where the chapter is written). This duplication does, however, mean that the chapters stand alone and can be read separately.

The book is up to date and is extensively referenced up to 1983, including the problem about etomidate producing cortisol suppression. There is the obligatory chapter on pharmacokinetics, and pharmacodynamics which, in this book, is confined to the barbiturates. This chapter, on p.29, launches into half times and clearance. It is not until p.225 that the appropriate equations are presented in the chapter on Minimum Infusion Rate, which may be confusing for the uninitiated.

When reviewing the usefulness of this book, it must be considered against other books on related topics. It is very up to date, and has much more information on the non-barbiturate agents than Dundee and Wyant's 1974 edition of *Intravenous Anaesthesia*. There is also some overlap with the April 1983 volume of *Clinics in Anaesthesiology*, which covers "Narcotic Anaesthesia" in a less comprehensive manner than the present volume. The pharmacology of fentanyl is dealt with in more detail in the earlier volume, but only covered in a short chapter on infusions in this current volume.

All the chapters in this volume are by experts in their field and reflect personal view-points of specific areas related to i.v. anaesthesia. Particularly impressive are the chapters on minimum infusion rate and adverse reactions. There is also a useful chapter on evaluation of i.v. anaesthetics in volunteers which describes in detail the setting up of a Phase I study for a new agent.

With the current unavailability of Althesin and propanidid and the uncertain future of etomidate infusions, some of the material in this book assumes a historical perspective.

The book is in hard back, and the only one available that covers the field. It is well referenced and contains much relevant recent information at a very reasonable price. In the absence of a new edition of Dundee and Wyant's book, it is to be highly recommended, although it lacks the overall cohesiveness of the earlier text. It is therefore a must for any department and an excellent source of information for examination candidates.

P. S. Sebel

Anaesthesia: Lecture Notes for Students. By M. Anis and M. Salim. Published by AFM College Press. Pp.135; illustrated.

These *Lecture Notes* have been compiled by the authors from lectures given at the Army Medical College, Rawalpindi, Pakistan, although the sections on History of Anesthesia and Pain are written respectively by J. Alfred Lee and John Bonica. The authors wisely point out in their Preface that, because of this variety in authorship, "the expressions and spellings, therefore, vary". Nevertheless, there is a major disparity of style in various parts of the book and there would seem little excuse for the wide variations in spelling that occur within individual chapters.

The content of the book may well be appropriate for its initially intended audience, but its appropriateness in the wider context is open to doubt. Much of the equipment and some of the techniques described are now of only historic interest to the U.K. student. On the other hand, there are fundamental items of equipment and anaesthetic methods to which no reference is made.

Some of the pharmacology is useful in that it is clearly described without too much detail and might help medical students obtain an initial overview of the subject, but agents which in the U.K. are no longer used occupy too much space and new agents are omitted. Thus, divinyl ether and ethyl chloride are both given space, but there is no mention of either enflurane or isoflurane. In the section on myoneural blocking drugs, tubocurarine and gallamine are the only non-depolarizing drugs mentioned! Moreover, the absence of an index makes it difficult to use as a reference.

One accepts that this book is deliberately produced on a low-cost basis, but the type-setting, production of the diagrams and overall presentation is poor, although no price is given for comparison. It is not a book that could be recommended to U.K. students, as the content is insufficiently relevant to their needs, although it may well be suitable for those for whom the contents were originally intended.

J. S. M. Zorab

Anaesthesia and Sedation in Dentistry. Monographs in Anaesthesiology. Edited by M. P. Coplans and R. A. Green. Published by Elsevier, Amsterdam. Pp. 421; indexed; illustrated. Price $57.50.

As the joint editors indicate in their foreword, the aim of this book is to give the medical and dental practitioners engaged in the field of anaesthesia and sedation a broader insight to topics of current interest.

The first three chapters rather belie this aim, as they concern themselves with established respiratory and cardiovascular physiology and the relative contraindications to anaesthesia. The content of these chapters will be very familiar to anaesthetic trainees from their reading of standard texts, but a dental graduate interested in anaesthesia might find the academic content helpful.

The editors themselves contribute two chapters, the first on the evolution of dental anaesthesia with perceptive comment on the contemporary scene and the second being a discussion of anaesthetic mortality in dental practice.

The first section concludes with a salutory chapter on medico–legal problems.

The second section of the book concerns itself with the problems of sedating patients undergoing dental procedures under local analgesia. It opens with a brief chapter on regional techniques and the commonly used analgesic drugs, which seems a little out of place, and the remaining chapters concern themselves with i.v. and inhalation sedation. That on inhalation sedation is an excellent account, but the chapter on i.v. sedation as practised in the United Kingdom and North America reveals the differences in viewpoint that always emerge when experienced dental practitioners and professional anaesthetists discuss sedation in the widest terms.

The concluding section contains five chapters on the use of general anaesthesia in both dental and facio–maxillary surgery and can be confidently recommended for a comprehensive account of present day clinical practice.

The main appeal of this book will be to postgraduate dental and medical practitioners actively engaged in sedation and anaesthesia. The career anaesthetic trainee will find the third section helpful to supplement the standard textbook. References are plentiful and in the main are of recent origin.

D. P. Braid

Nursing the Patient in Pain. By Margo McCaffery. Published by Harper and Row. Pp. 426; Indexed; illustrated. No price given.

Miss McCaffery has produced a well documented book which outlines the steps to take in dealing with one of the most consistent problems presented to nursing staff—that of the patient in pain.

She stimulates nurses to think positively and imaginatively about the variety of methods to relieve pain, instead of merely resorting to either tablets or injections: such methods as imagery, hypnosis, massage, relaxation, yoga, etc. She describes these in full and provides a short summary at the end of each chapter.

Although some nurses and patients tend to implement many of her methods without identifying them as such, I fear that the British culture, as it is, would feel they would obtain more benefit from a tablet or injection than from nurse telling them to "imagine themselves on a sun-drenched beach with clear warm water rolling gently over the sand!" I would go as far as to say that some of the usual "clients" found within my own hospital would probably suggest that the nurse should consult the local psychiatrist to have her head examined!

Patient education would have to be undertaken before any advances would be made in implementing Miss McCaffrey's suggestions. Having said this, there is much to be gained from re-examining our methods of giving pain relief in the light of the information delivered by Miss McCaffery's book.

E. McMillan

Drugs in Anaesthetic Practice. Edited by M. D. Vickers, H. Schnieden and F. G. Wood-Smith. Published (1984) by Butterworths, London, Boston. Pp. 607; indexed, illustrated. Price £33.00.

This well known textbook has been with us since 1962, and now appears in its sixth edition, which is itself a credit to its popularity and to the energy of its authors.

Now, however, it has competitors, and while cheaper than its American rival, it is more expensive but also longer than its British one. Does it stand up, as a textbook of pharmacology for anaesthetists, and does its greater length make it a better buy?

Clinical anaesthetists sometimes lose track of the pharmacological principles they should have learnt as medical students, but the pharmacologist Harold Schnieden who now appears as a co-author should ensure that sound basic pharmacological principles are adhered to throughout the book. As before, Conway, Fletcher, Horsey and Williams provide excellent contributions on inhalation agents, anticoagulants, infusion fluids and antimicrobial agents, respectively. In addition, the section on anticonvulsants is good, and the diagrams of the cardiac action potential are very clear.

With these exceptions, however, which are succinct and informative, the book could, with profit, be shorter. For example both structural formula *and* chemical name are supplied for the majority of drugs, as in a pharmaceutical publication. If either one of these is comprehensible to the reader, the other must be redundant, but there is little explanation of the implications of chemical configuration. A number of structural formulae are given twice (for example four of the benzodiazepines) and some are actually wrong. For example, the piperidine ring of morphine (a common feature of many opioids, although this is not pointed out by the authors) has been changed to a pyrrolidine ring, while in certain opioids the whole morphine skeleton has been turned on its side, so disguising the similarities. Tubocurarine is given as a bis-quaternary ammonium compound, contrary to current views.

Another source of length—the appendix of 42 pages comprising six alphabetical tables: (1) U.K. approved and trade names (the latter could with benefit be supplied in the text) with U.S. approved and trade names. (U.S. names *are* given in the text as well.) (2) U.K. approved and trade names (therefore identical to the left hand columns of table (1)). (3) U.K. trade and approved names and (4) and (5) U.S. approved and trade names and *vice versa*.

Is the text itself informative? Here, I find it necessary to cite a few examples. In the section on general pharmacology most kinetic functions are neither clearly defined, nor indexed. The *dose–response* curve is stated to be sigmoid (have the authors ever tried to draw one?). The authors warn us to "be aware of the trap associated with the word potency" and fall straight into it themselves by saying "drug A is more potent . . . since it has a higher ceiling effect" and that the potency of pethidine is between those of morphine and codeine, and more surprising still, chlorpromazine is more potent than fluphenazine and haloperidol. Efficacy is, of course, the pharmacological term to use in these contexts. Also, there is repeated use throughout the text of tautological phrases such as "weight for weight it is more potent".

The authors' use of the term "highly basic on solution" suggests confusion between a *basic group* and an *alkaline solution*. In the solution on protein binding, albumin only is mentioned, and the all important α_1-acid glycoprotein that binds numerous basic drugs, is omitted. Describing an ester linkage as C–O–C is confusing as this could apply equally to an ether. Elimination of drugs appears under the heading of absorption, while some parts of the legal section are out-of-date and others confused.

Some statements are misleading, for example the implication that thiopentione is taken by mouth, that drugs are *excreted* in saliva (which is normally swallowed): that if the volatile agent removed by the patient at each breath is replaced, *constant* rate absorption occurs—have the authors forgotten that the body gradually saturates?

The second chapter describes premedicants, mentioning many drugs the pharmacological properties of which are only described in later chapters. Throughout, in the descriptions of the drugs, there is confusion between pharmaceutical preparations and active drugs, with the implication that salts of the drugs exist in the body and exert effects. Headings are thereby rendered clumsy, and why "phenytoin *sodium*" and "*sodium* valproate"? More dangerous: dosage is often given as simply "adult dose", rather than as mg kg^{-1}. Individual drugs are listed within each group in alphabetical order (again like a textbook of pharmacy), thus, for example, buprenorphine comes before morphine. Also, inconsistent details are given. Thus, with promethazine "arrhythmias do not occur". Do they with other phenothiazines, or is promethazine *anti*-arrhythmic? Thrombophlebitis is mentioned in connection with thiopentone. Do other induction agents not cause it? Indomethacin acts independently of the pituitary–adrenal axis. Do other NSAIDS not? Other aspects of organization might seem confusing. For example: metoclopramide appears in the middle of the sedatives, digitalis *under* digoxin, etidocaine *under* lignocaine, reserpine among the sympathomimetics, papaveretum *not* under morphine, diisopyramide under drugs affecting coronary blood vessels. In the section on CNS depressants, major and minor tranquillizers are not defined, but described together so that the student might believe benzodiazepines cause extrapyramidal disturbances. The dependence liability of the benzodiazepines is stated to be low, and the production of active metabolites advantageous—surely a dangerous misconception.

In the section on opioids, their mode of action on opiate receptors is not described; the half-life of fentanyl is given as 20 min, with no mention of the fact that it has a bolus effect and a *long* terminal half life—this omission in *dangerous*. The description of methadone is contradictory; nalorphine and levallorphan (and elsewhere even chloroform) are referred to as if they were in current use while devotees of spinal morphine will be interested to hear it has a strychnine-like effect on the spinal cord!

Local anaesthetics are described as being active as the free base, and the most common side effects those of atropine. Their breakdown is said to depend on liver function, instead of liver blood flow, and convulsions should be treated with thiopentone, with oxygen only mentioned as an afterthought. A single oil/water (*sic*) partition coefficient is given which, as such, is meaningless.

There is no overall description of the autonomic nervous system, with no clear statement that noradrenaline is the transmitter at adrenergic nerve endings. Postganglionic parasympathetic vagal (*sic*) nerves are said to dilate blood vessels, and β_2 stimulation is said to cause tachycardia. Excess parasympathetic activity is said to be helpful in an emergency. The cardiovascular section is a trifle jumbled and perhaps in places even misleading. Is theophylline often used to treat angina? As an anti-arrhythmic, lignocaine gets mentioned only in a table, which in no way differentiates its action from a classic quinidine-like effect. Prostaglandins are described in two separate chapters, where a single comprehensive description might have been more helpful. Oxytocin is said to be readily absorbed orally, and to be more effective than ergometrine as a uterine stimulant in *early* pregnancy. Despite frequent use of the term "ADH" elsewhere in the text, it does not appear as such under the heading of vasopressin. Oral hypoglycaemics, which are surely important to anaesthetists, are given 8½ lines of text, and no formulae, while mild analgesics and NSAIDs are given 13 pages, nine structural formulae and all the frills.

It is truly remarkable that, during the present explosion of scientific knowledge, the same principal author can produce textbooks for anaesthetists on pharmacology, medicine and clinical measurement. Such is, indeed, a Herculean task, which in this text at least is not satisfactorily achieved.

F. Reynolds

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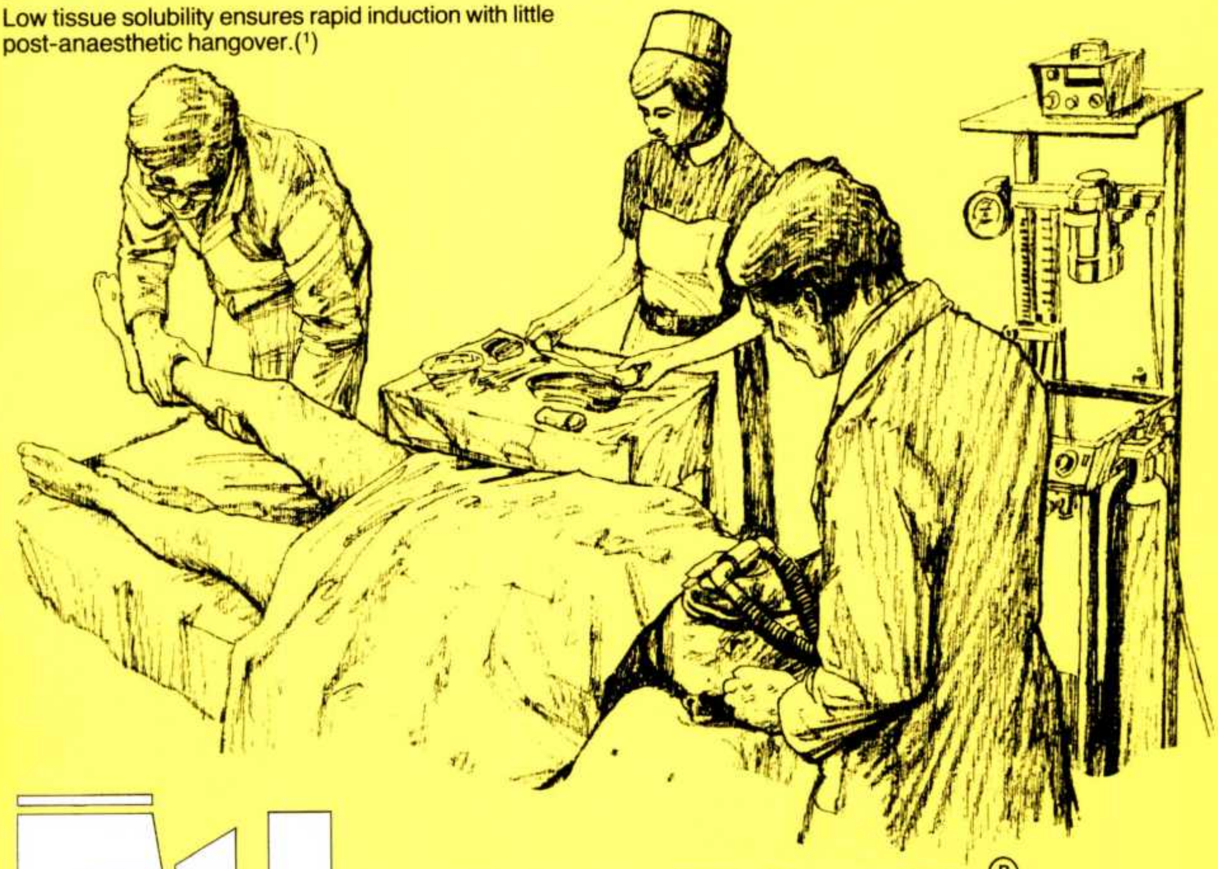

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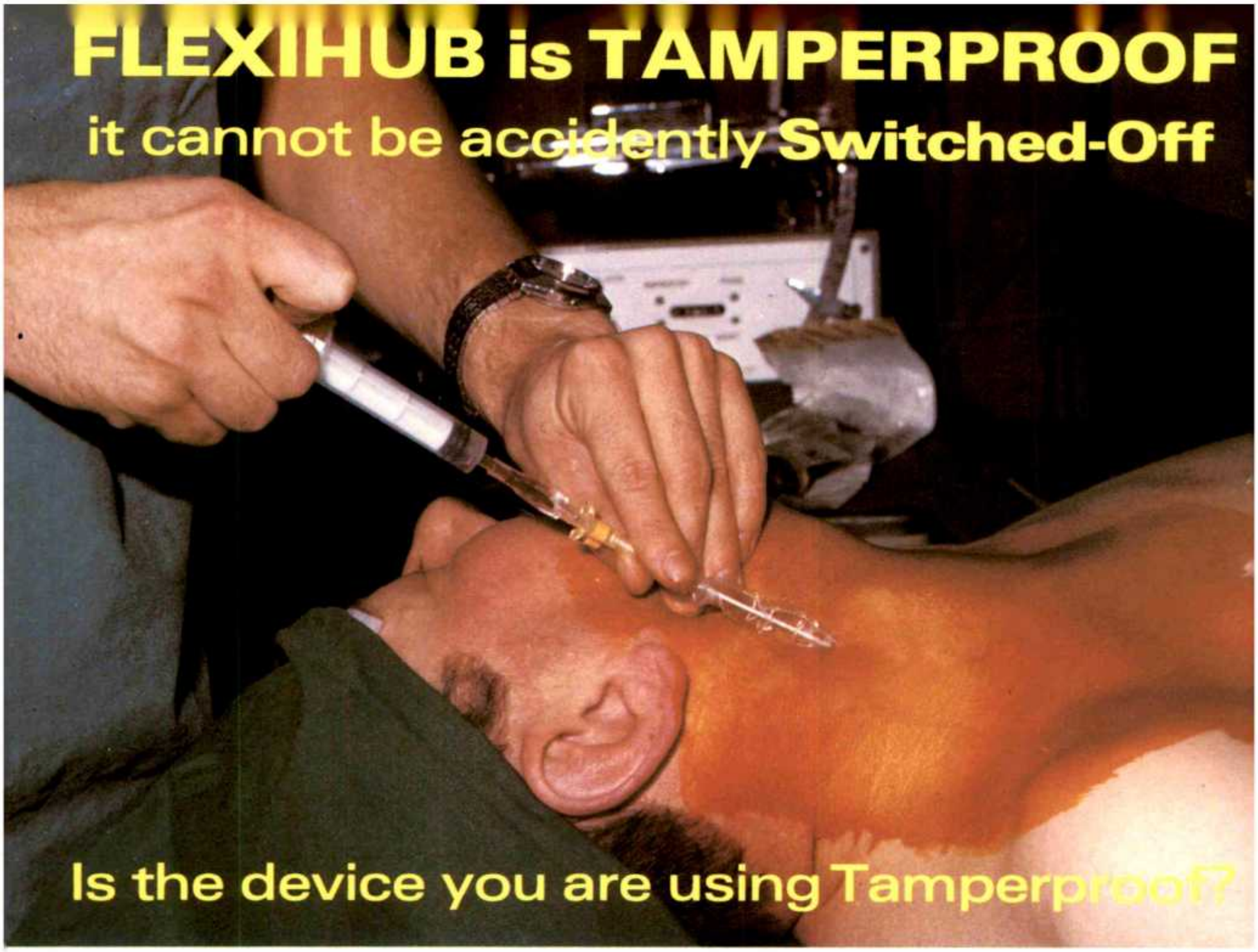
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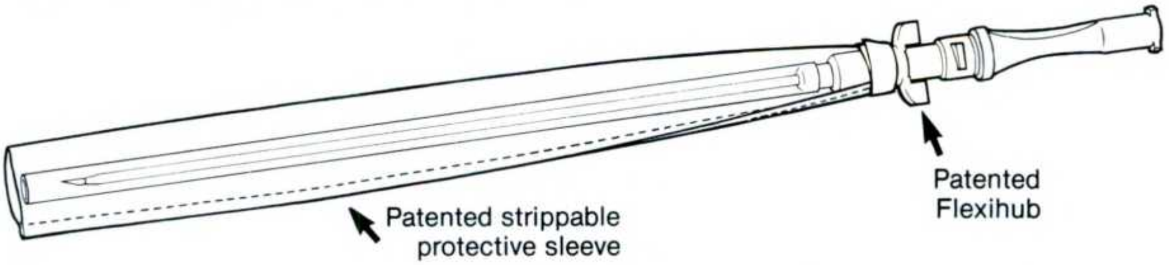

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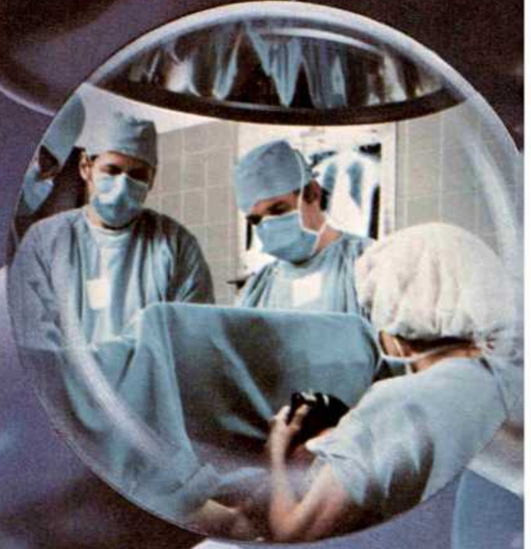

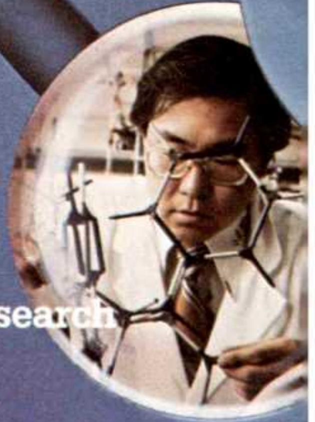

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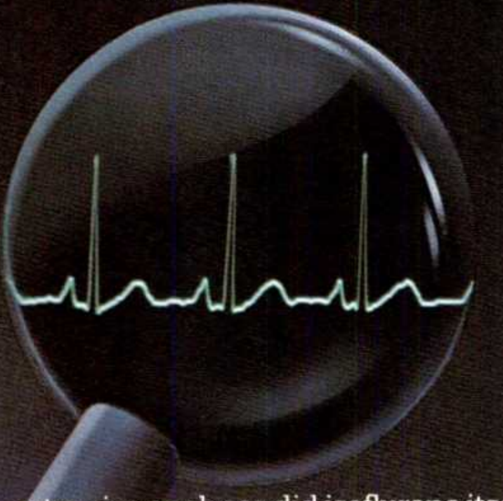

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NORCURON ampoules of 4mg vecuronium bromide with 1ml ampoule water for injection. **Uses:** non-depolarising neuromuscular blocking agent of short to medium duration. **Dosage:** intravenous initial 0.08 to 0.10mg/kg incremental 0.03 to 0.05mg/kg. **Contra-indications:** none known. Since there is no experience of NORCURON in pregnant women it cannot be recommended in such cases or in childbirth. **Precautions and warnings:** in renal insufficiency a slight prolongation of neuromuscular block can be expected. Use very small doses, and extreme caution in myasthenia gravis or myasthenic syndrome unless prolonged post-operative respiratory assistance is intended. Dose carefully in myopathy, severe obesity, electrolyte disturbances, altered pH and after poliomyelitis or dehydration. Neuromuscular blockade can be reversed with adequate doses of neostigmine together with atropine. **Interactions:** it is dangerous to give depolarising drugs (e.g. suxamethonium chloride) following a non-depolarising drug (e.g. Norcuron). Alkylating drugs (nitrogen mustards) may be a hazard in anaesthesia involving muscle relaxants. Anaesthetics, other drugs and the condition of the patient, may affect the magnitude and or duration of action of NORCURON — see Data Sheet. **Side-effects:** none during clinical testing. **Overdosage:** use standard reversal agents, e.g. neostigmine or pyridostigmine. **Packs:** 50 ampoules 4mg NORCURON, 50 amopules 1ml solvent. **PL:** 3524/0009.

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Title page
Summary
Introduction (not headed)
Methods
Results
Discussion
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List of references
Tables
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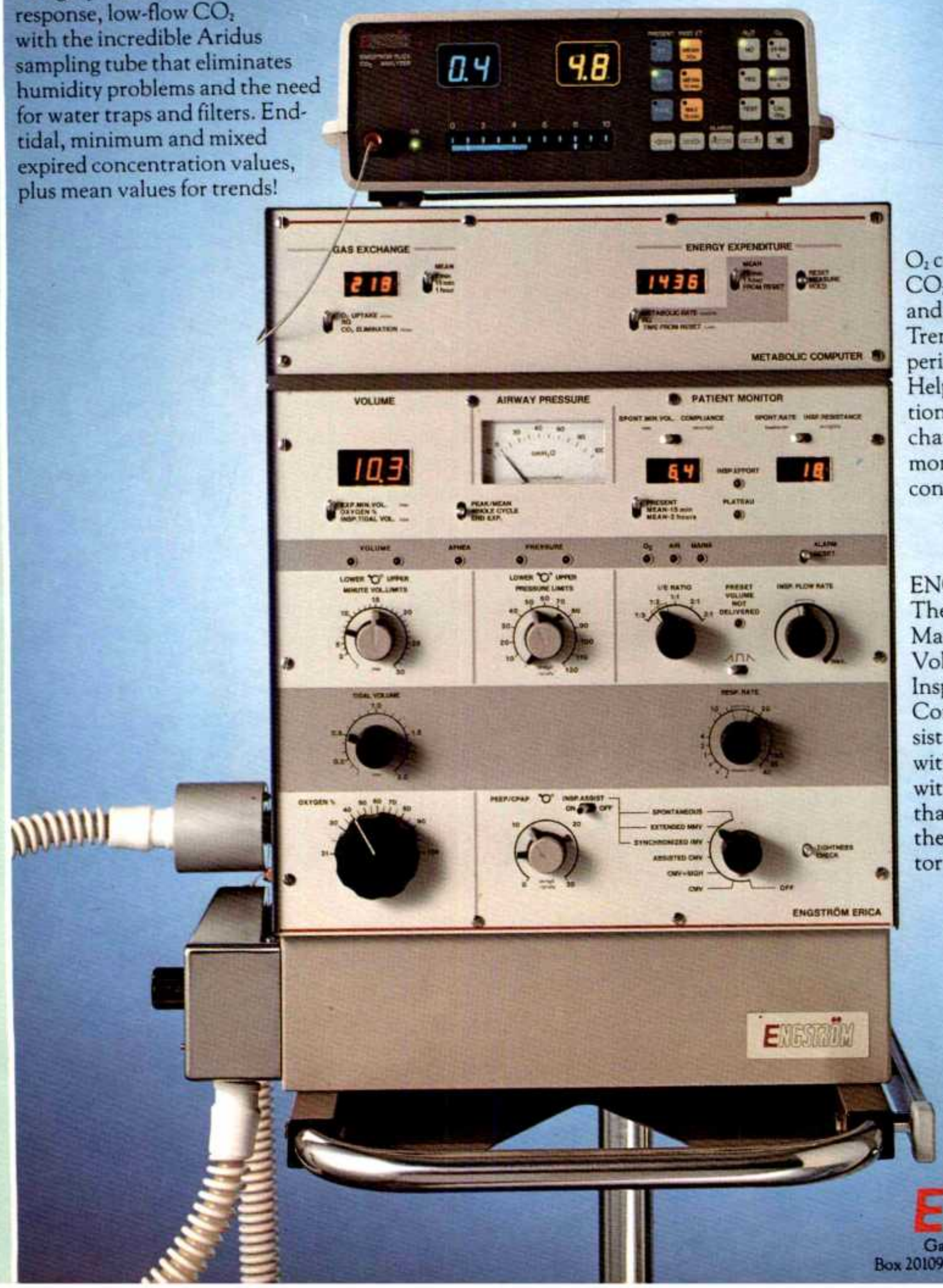

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It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

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These should be corrected and returned to the sub-editor *within 48 hours of receipt.* Overseas contributors should return their proofs by airmail.

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June 16–21, 1985 Athens, Greece

Aims and Scope: The state of current knowledge will be examined regarding the functional aspects of muscle physiology and the mechanics of muscle. Particular relevance to applications in clinical medicine, especially in the area of cardiovascular, pulmonary, orthopaedic and neurological assist devices. Particular attention will be given to the electrical stimulation of the muscle.

Programme: Papers will be presented in the morning, followed by a luncheon discussion.

Information from:
Dr Anthony Sances, jr,
Department of Neurosurgery,
The Medical College of Wisconsin,
8700 West Wisconsin Avenue,
Milwaukee, Wisconsin 53226 U.S.A.

XIIth CONGRESS OF THE EUROPEAN SOCIETY FOR ARTIFICIAL ORGANS

AND

INTERNATIONAL DIABETES FEDERATION PRE-CONGRESS MEETING

September 16–19, 1985 Athens, Greece

In conjunction with the ESAO 12th Congress, the IDF Pre-Congress meeting will consider the artificial endocrine pancreas, insulin delivery devices and pancreas and islet transplantations. The meetings will include invited lectures, workshops and a number of free communications (oral and poster presentation). Congress language will be English.

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September 20–21, 1985 Brussels

Venue: Institute of Sociology, Université Libre de Bruxelles.

Scientific Committee: G. Black (Belfast), F. Camu (Brussels), J. Dubois-Primo (Brussels), M. J. M. Govaerts (Brussels), B. Gribomont (Brussels), W. Hain (Nottingham), D. Hatch (London).

Main Topics: Artificial ventilation in children under 5 years of age; pre-, per- and postoperative care of the infant; problems in anaesthesia and intensive care in children.

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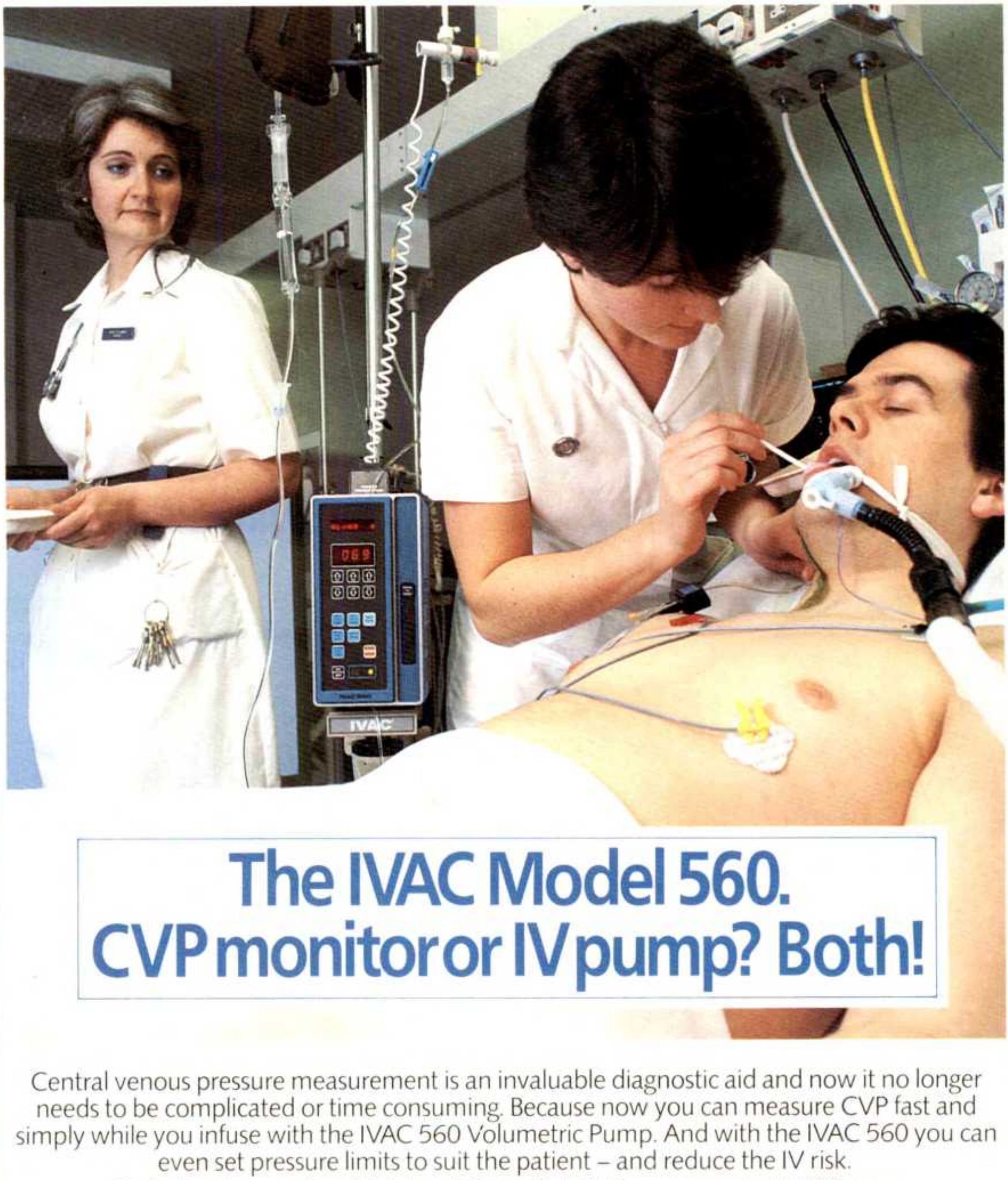

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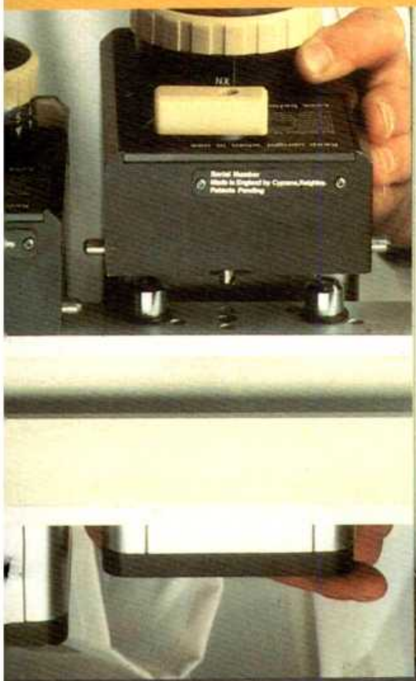

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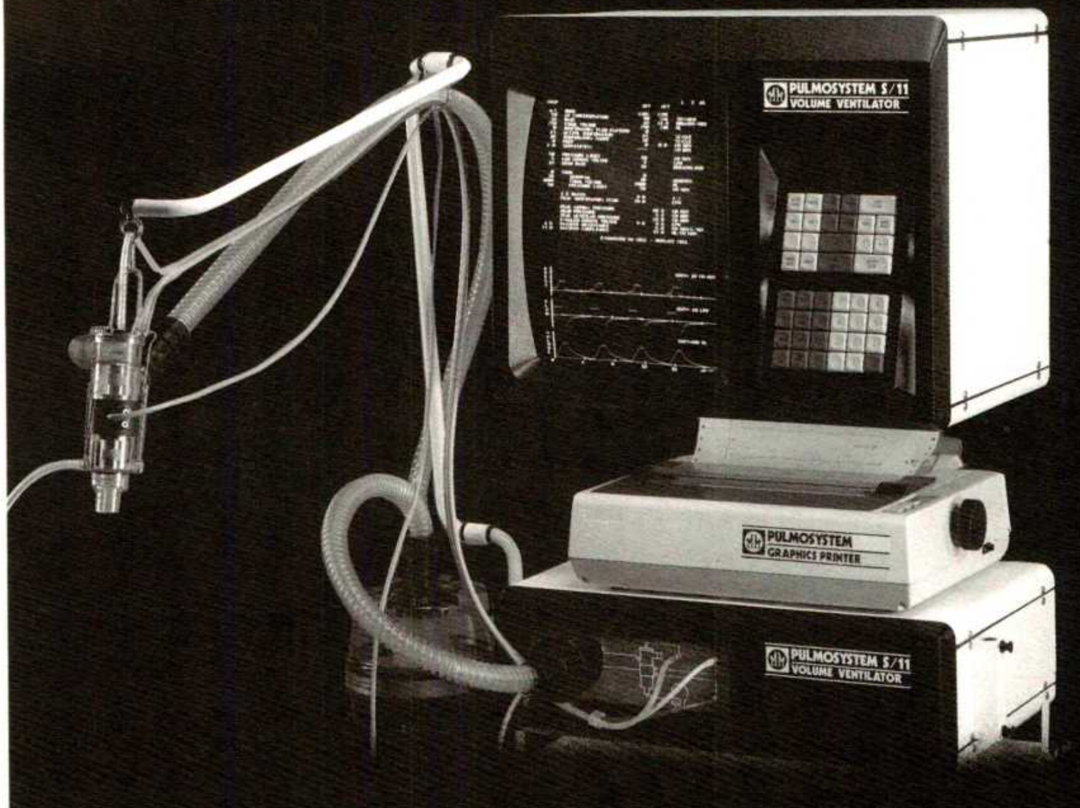

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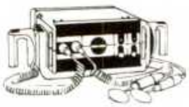
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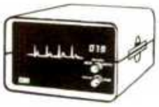
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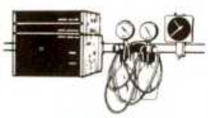
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ISOFLURANE AS A ROUTINE ANAESTHETIC IN GENERAL SURGICAL PRACTICE

J. F. NUNN

SUMMARY

One hundred and thirty-five consecutive patients (aged 2 months to 95 yr) were anaesthetized with isoflurane for routine surgery in a District General Hospital. No major problem was encountered. One patient in the series developed ventricular extrasystoles (1 min^{-1}), although 22 patients received a mean dose of adrenaline 3.35 μg kg^{-1}. Seventeen patients had pre-existing myocardial ischaemia or angina, but there was no electrocardiographic evidence of ischaemia developing during anaesthesia. There was a mean increase in heart rate of 5 beat min^{-1} during anaesthesia although the maximum values reached 200 beat min^{-1} in children, and 150 beat min^{-1} in adults who received fazadinium and 140 beat min^{-1} in adults who did not. Supplementary doses of neuromuscular blocking drugs were seldom needed, and never for closure of peritoneum. There was a very low incidence of untoward events during recovery, although two patients early in the series showed delirium, probably as a result of sudden perception of pain following the rapid recovery. The mean half-time of wash-out of alveolar isoflurane (two patients) was 27 s. The mean volume of isoflurane administered per patient was 22 ml of liquid using fresh gas flow rates in the range 6–9 litre min^{-1}.

Isoflurane became available in the United Kingdom at the end of 1983. Since 1971 there has been a greater volume of publications on the pharmacology of this agent than has preceded the advent of any other anaesthetic agent. In contrast, however, there have been relatively few publications describing its clinical use and, in particular, there has been no account of its use in the United Kingdom, where the circumstances of surgery and clinical anaesthesia differ in many respects from North America, where it has been in general use since 1982. Thus, it appeared appropriate to give a brief account of its routine use in a British District General Hospital during the period from late 1983 to early 1984.

PATIENTS AND SURGERY

During the period of this study, isoflurane was used for every patient whom the author anaesthetized and its use was continued in all except two patients until shortly before the end of surgery. Since isoflurane had a product licence, its use for general anaesthesia was regarded as routine clinical practice, and no approach was made to the ethics committee. All anaesthetics were administered either by the author or by a trainee under his direct supervision.

The series comprised 135 consecutive patients ranging in age from 2 months to 95 yr (table I). All surgery was elective and the patients were predominantly in ASA groups I, II and III (table II). The incidence of concomitant disease is shown in table III, and medication prescribed before operation, in table IV. The range of surgical operations was governed by the repertoire of the surgeons with whom the author works and did not include gynaecological, obstetric, orthopaedic, otorhinolaryngological, ophthalmic, cardiac, thoracic or neurosurgical procedures (table V).

ANAESTHESIA

Premedication

Most adults received papaveretum 10–20 mg and hyoscine 0.2-0.4 mg. In patients older than 60 yr, the hyoscine was replaced by atropine 0.6 mg. Phenergan 25 mg, atropine 0.6 mg and pethidine 50mg were used in three patients with asthma or chronic bronchitis. A few patients for repeat cysto-

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J. F. NUNN, M D, PH D, F R.C.S, F.F A R.C.S, F.F A R A.C.S.(HON), Division of Anaesthesia, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ.

TABLE I. *Distribution of ages of patients*

Age	No.
0-12 months	4
1-10 yr	8
11-20 yr	7
21-30 yr	4
31-40 yr	19
41-50 yr	11
51-60 yr	26
61-70 yr	29
71-80 yr	22
81-90 yr	4
91-100 yr	1
Total	135

TABLE II. *Distribution of ASA risk factors*

Factor	No.
ASA Group I	82
ASA Group II	27
ASA Group III	19
ASA Group IV	7
ASA Group V	0
Total	135

TABLE III. *Incidence of concomitant disease*

Disease	No.
Myocardial ischaemia/angina	17
Hypertension	8
Bronchitis and emphysema	6
Diabetes	6
Asthma	6
Cardiac arrhythmia	4
Epilepsy	3
Obesity	3
Intermittent claudication	2
Cerebrovascular accident	2
Valvular heart disease	2
Still's disease	1
Congenital heart disease	1
Aneurysm of aorta	1
Thrombocytopaenia	1
Anaemia	1
Hypercalcaemia	1
Pyrexia of unknown origin	1

scopy were content with either no premedication or oral temazepam 10–20 mg. The four children younger than 1 yr received, respectively, no premedication, atropine 0.1 mg (two children) and 0.2 mg (one child). Children between the ages of 2 and 7 yr received trimeprazine 3 mg kg^{-1}, by mouth, followed by papaveretum 3–5 mg and hyoscine 0.06–0.1 mg i.m. They arrived in the anaesthetic room asleep but rousable.

TABLE IV. *Incidence of patients receiving medication before operation. One patient had a pacemaker*

Premedication	No.
Beta-adrenergic blockers	11
Diuretics	10
Salbutamol	6
Steroids	5
Calcium channel blockers	5
Anti-hypertensives (other than above)	4
Oral hypoglycaemics	4
Cardiac glycosides	3
Glyceryl trinitrate	3
Thyroxine	3
Aminophylline	2
Anti-epileptic drugs	3

TABLE V. *Operations*

Operation	No.
Thyroid and parathyroid	11
Renal	12
Cholecystectomy	7
Laparotomy	9
Procedures on the groin	21
Prostatectomy	9
Breast surgery	18
Circumcision	4
Cystoscopy	32
Miscellaneous	12
Total	135

Induction

All patients older than 7 yr received thiopentone 100–400 mg. The 11 patients younger than 8 yr received an inhalation induction using isoflurane vaporized in oxygen.

Maintenance

Neuromuscular blocking drugs were administered to 59 patients (table VI), no patient receiving more than one such drug. Suxamethonium was used to facilitate the passage of a tracheal tube in four patients, who then breathed spontaneously. In the remaining 55 patients, all adults, the lungs were ventilated artificially, anaesthesia being maintained with isoflurane vaporized in 65% nitrous oxide in oxygen using a non-rebreathing system and a Manley ventilator set to deliver a minute volume of 6–9 litre min^{-1}. The mean duration of the administratin of isoflurane in patients ventilated artificially was 87 (SD 24) min.

The 71 patients older than 5 yr who breathed spontaneously received isoflurane vaporized in 65% nitrous oxide in oxygen using a Magill system with a

TABLE VI. *Patients receiving neuromuscular blocking agents*

	No. of patients	Total dose ($mg\ kg^{-1}$)		Duration of op. (min)	
		Mean	SD	Mean	SD
Pancuronium	12	0.096	0.020	95	24
Fazadinium	6	1.2	0.14	93	9.4
Alcuronium	17	0.28	0.11	82	20
Atracurium	14	0.67	0.28	78	26
Vecuronium	6	0.15	0.06	83	54
Suxamethonium	4	—	—	—	—
Total	59				

fresh gas flow sufficient to prevent rebreathing. Nine patients younger than 6 yr received the same mixture from a Jackson Rees T-piece system. The inspired concentration of isoflurane was adjusted to prevent spontaneous movement in response to surgical stimulation. The duration of administration of isoflurane ranged from 10 to 75 min in all except one patient, in whom it was 165 min. Excluding this patient, the mean duration was 32 (SD 26) min.

TABLE VII. *Total dose of adrenaline administered by surgeons before incision*

Dose (mg)	No. patients
0.1	2
0.15	3
0.2	9
0.25	2
0.3	3
0.35	2
0.5	1
Total	22

Analgesia

For relief of early postoperative pain, eight patients received regional blockade with bupivacaine before incision. These were mainly intercostal nerve blocks in patients scheduled for cholecystectomy (0.5% bupivacaine 20 ml) and penile blocks for those requiring circumcision. In a further 11 patients, the area of the incision was infiltrated with 0.25% bupivacaine at the end of the operation. The only opiate used during operation was morphine and this was administered towards the end of the operation in 13 patients in a mean dose of 5 mg (SD 2 mg).

Adrenaline

The surgeons infiltrated the line of the incision with 1:200 000 adrenaline for most patients undergoing thyroidectomy, parathyroidectomy or nephrectomy. Twenty-two patients received a mean dose of adrenaline 3.35 $\mu g\ kg^{-1}$ (SD 1.12) (table VII).

Monitoring

The electrocardiogram was observed on a monitor screen (CM 5 lead) during surgery in 110 patients. Arterial pressure was measured either by the Riva Rocci method or with an oscillotonometer. Heart rate was measured electrically from a pulse signal derived from optical transmission through the lobe of the ear.

The vaporizer

The same Cyprane vaporizer calibrated for isoflurane was used for both induction and maintenance throughout the series. It was also calibrated in our own laboratory and found to deliver concentrations within 10% of dial readings, at the carrier gas flow rates used in the study. The error was high at settings of 1 and 2% and low at settings from 3 to 5%. The rate at which the delivered concentration decreased when the level of isoflurane decreased below the bottom of the sight glass was measured during a continuous flow of nitrous oxide 4 litre min^{-1} + oxygen 2 litre min^{-1} at a setting of 3% using a Datex Normac infra-red analyser. Gradients of isoflurane concentration in the gas system resulting from loss of isoflurane into the rubber parts of the system were measured using the same analyser, which was also used for measuring the rate of decrease of the end-tidal isoflurane concentration when the inspired concentration was reduced from 1% to zero.

RESULTS

There was no mortality in the series and no significant morbidity attributable to anaesthesia. There was no indication that any patient had recall of events during anaesthesia or surgery.

Inspired concentrations of isoflurane

In the patients receiving neuromuscular blocking drugs and artificial ventilation, the initial setting for the inspired isoflurane concentration was 1% and remained at this value until shortly before the end of the operation in 19 patients. Concentrations of isoflurane were increased for all or part of the anaesthetic in 19 patients (table VIII). In nine patients this was because the arterial pressure appeared to be increasing in response to surgery (mean systolic pressure 150 mm Hg). Concentrations of isoflurane were decreased for all or part of the anaesthetic in 19 patients, in five of whom the arterial pressure appeared to be decreasing in response to anaesthesia (mean systolic pressure 72 mm Hg). In the remaining 14 patients, a lower concentration was used because of a clinical assessment of the requirement of isoflurane for a particular patient without any objective indication of the necessity for the use of the lower concentration.

TABLE VIII. *Inspired concentrations of isoflurane during anaesthesia with neuromuscular blockade and artificial ventilation. (Some patients feature in more than one category)*

Isoflurane concentration	Patients
Maintained at 1% throughout	19
Decreased to 0.5%	17
Decreased to zero	2
Increased to 1.5%	8
Increased to 2%	8
Increased to 2.5%	1
Increased to 3%	2
Total	57

Patients who were able to breathe spontaneously and had received thiopentone were able to tolerate an initial inspired concentration of 2% isoflurane without coughing. This could then be increased to 4 or 5% within the course of about 1 min. Children who had not received thiopentone would tolerate 1% initial inspired concentration whether asleep or awake and this could be increased progressively to 4% within about 90 s, loss of eyelash reflex usually occurring within the same time. It is not possible to relate inspired concentrations to the time to loss of consciousness with any precision because, initially, the mask was held clear of the face in the sleeping children and, therefore, the actual inspired concentration at this time was in doubt. However, induction was clearly very rapid.

During the maintenance of anaesthesia with spontaneous breathing, the inspired concentration was adjusted to prevent response to surgical stimulus, and experience of the required concentration increased as the series proceeded. The mode of the maximal concentration was 2%, but ranged from 1 to 4% (table IX). Concentrations of 3 or 4% were used on four occasions because the systolic arterial pressure had increased to 160 mm Hg or above. In the other patients it was used for short periods of time in anticipation of severe surgical stimulation (e.g. circumcision), and in children in whom higher concentrations were needed generally to secure surgical anaesthesia.

TABLE IX. *Maximal concentration of isoflurane required during maintenance of anaesthesia without neuromuscular blockade. (Records were incomplete in 15 patients)*

	Concentration of isoflurane	No. patients
	1%	4
	1.5%	8
	2%	31
	2.5%	3
	3%	13
	4%	6
Mean	2.3%	
SD	0.85%	
Total		65

The response to changing the inspired concentrations was very rapid, such that the depth of anaesthesia could be increased rapidly, and the arterial pressure controlled readily.

Recovery and time-course of wash-out of alveolar isoflurane

Very little time was available for tracheal intubation under isoflurane in patient number 100 (aged 2 months) because of the rapidity of lightening of anaesthesia when the mask was removed from the face before laryngoscopy. Three wash-out curves were recorded in two adults during artificial ventilation after a minimum of 1 h of inhalation of 1% isoflurane (fig. 1). The mean half-time of the rate of reduction of alveolar isoflurane was 27 s. Most patients were rather heavily premedicated and no attempt was made to achieve rapid awakening from anaesthesia. However, 14 patients were responding

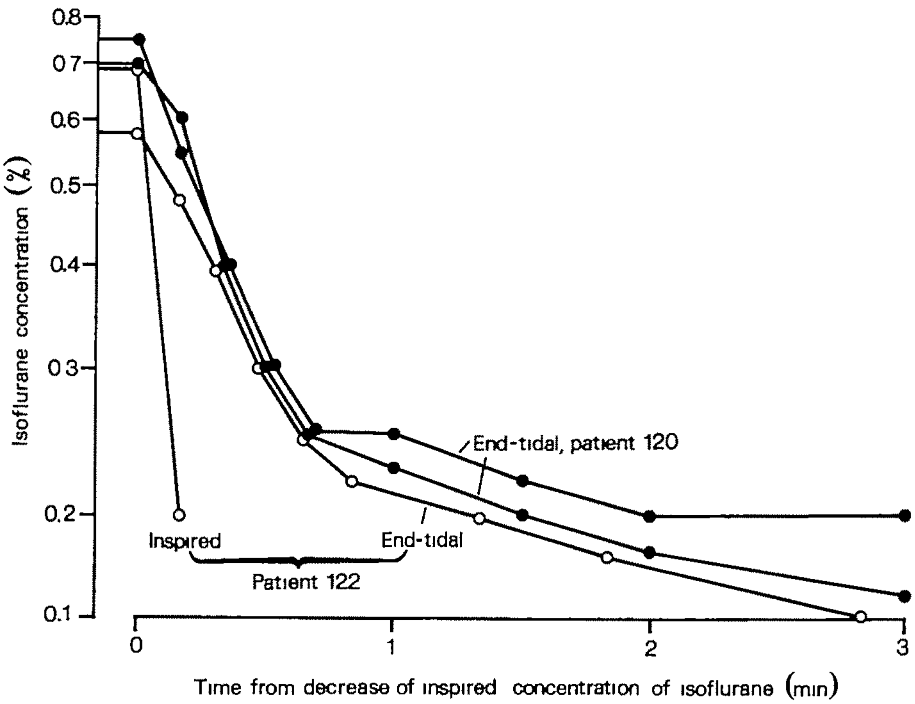

FIG 1. Wash-out curves for alveolar isoflurane, obtained during artificial ventilation with nitrous oxide in oxygen gas mixture after 1 h of equilibration with an inspired concentration of 1% isoflurane vapour. Two runs were made with patient No. 120 and one with patient No. 122, for whom the rate of change of inspired concentration is also shown.

to commands within 5 min of the end of inhalation anaesthesia and a further 27 within 10 min.

Heart rate

The mean heart rate before induction was 78.4 (SD 17.5) beat min^{-1}. During anaesthesia, the time-weighted mean rate was 83.4 (SD 24.6) beat min^{-1}, the difference being just significant ($P = 0.05$). Before induction, heart rates were much higher in children up to the age of 10 yr (mean 111.7, SD 24.2 beat min^{-1}). During anaesthesia, the time-weighted mean rate was 131.7 (SD 36.3) beat min^{-1}, the difference being significant ($P < 0.05$).

There was a very variable response to the anaesthetic. In 46 patients, the rate did not change by more than ± 10 beat min^{-1} from the preoperative value (fig. 2). In 38 patients, the minimal rate during anaesthesia decreased to less than the preoperative value by more than 10 beat min^{-1} and in 51 the maximal value increased above the preoperative value by more than 10 beat min^{-1} (excluding measurements after atropine in the course of reversal of a neuromuscular blocking drug). In 92 patients the fastest heart rate during anaesthesia was in the range 60–100 beat min^{-1} (excluding the period of administration of atropine before reversal of neuromuscular blockade). However, the range extended upwards to 150 beat min^{-1} in adults and 200 beat min^{-1} in children (fig. 3). The patients with the highest rates and the greatest changes are shown in table X and figure 4.

Arterial pressure

In most patients, arterial pressure responded rapidly to changes in the inspired concentration of isoflurane and, with neuromuscular blockade and artificial ventilation, the pressure could be controlled readily by alterations in the inspired isoflurane concentration. In patients ventilated artificially the systolic pressure decreased to 60 mm Hg in two patients, 70 mm Hg in eight, and 80 mm Hg in 10 patients. Significant increases in arterial pressure occurred in two patients (fig. 5). In patient No. 117, the increases in arterial pressure were not fully con-

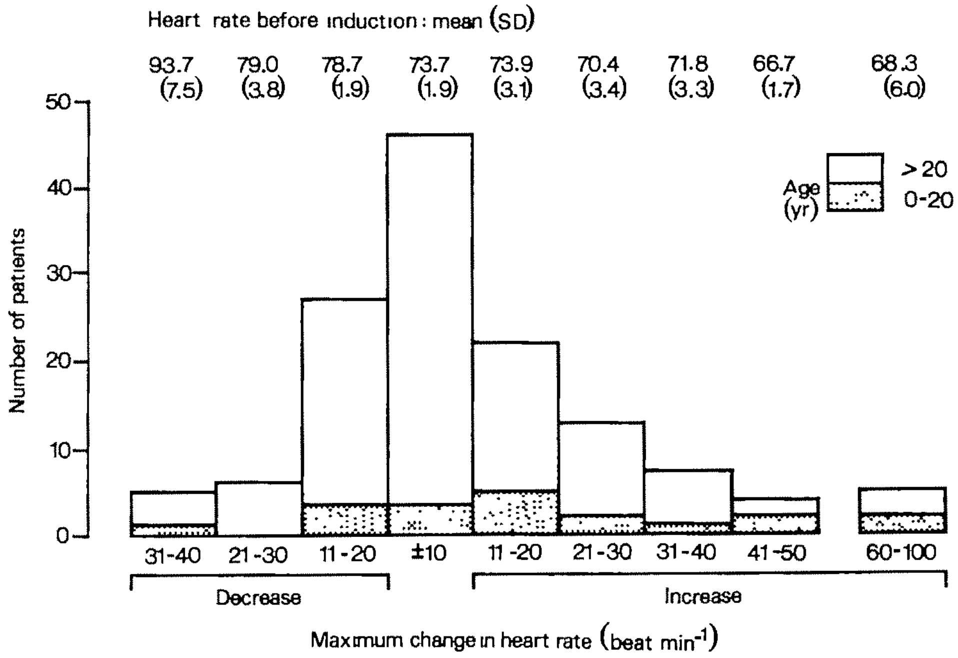

FIG. 2. Histogram of maximal changes from pre-induction heart rates (excluding observations made after administration of atropine before the use of neostigmine). There is a negative correlation between the change for each group and the mean heart rate before induction ($r = -0.83$).

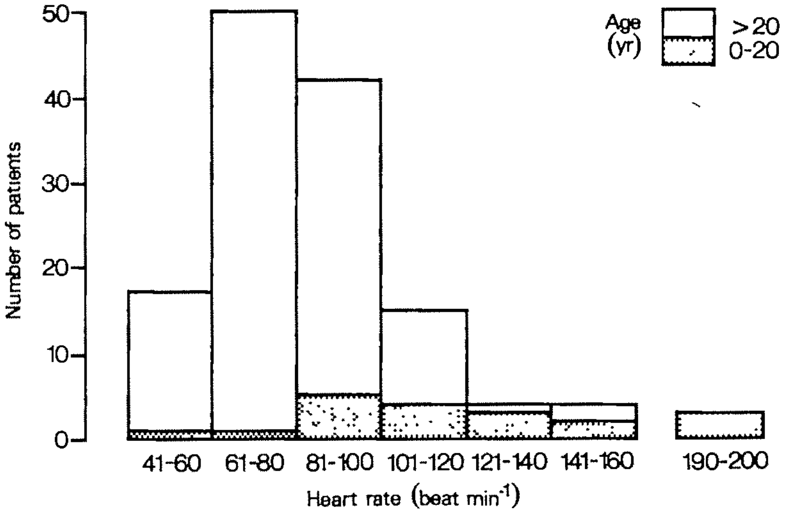

FIG. 3. Histogram of maximal heart rates observed during anaesthesia (excluding observations made after administration of atropine before the use of neostigmine).

TABLE X. *Patients with maximal heart rates during anaesthesia > 120 beat min^{-1} or increases in rate > 40 beat min^{-1} following induction, or both. *See figure 4. Pap. = papaveretum; Hy. = hyoscine; Trimep. = trimeprazine*

								Heart rates		
									Highest	
	Serial No.	Age	Sex	Operation	Premed.	Myoneural blocker	Adrenaline infiltration	Before op.	During op.	After op.
Rates > 120 beat min^{-1} and increase in rate > 40 beat min^{-1}	132*	2/12	M	Herniorraphy	Atropine 0.1 mg	—	—	140	190	200
	100*	2/12	M	Hydrocele	Atropine 0.1 mg	—	—	100	200	100
	40	52	F	Thyroidectomy	Pap. 15 mg Hy. 0.3 mg	Fazadinium	0.2 mg	60	150	70
	135*	5	M	Circumcision	Trimep. 60 mg Pap. 5 mg Hy. 0.1 mg	—	—	100	180	120
	47	47	M	Thyroidectomy	Pap. 20 mg Hy. 0.4 mg	Fazadinium	0.5 mg	65	150	75
	45*	22	M	Splenectomy	Pap. 20 mg Hy. 0.4 mg	Alcuronium	—	80	140	120
Rates > 120 beat min^{-1} but increase in rate < 41 beat min^{-1}	75	4/12	M	Exploration of groin	Atropine 0.2 mg	—	—	130	150	160
	125	2	M	Orchidopexy	Trimep. 30 mg Pap. 3 mg Hy. 0.06 mg	—	—	110	150	120
	115	5/12	M	Circumcision	Nil	—	—	160	140	140
	80	2	M	Circumcision	Trimep. 45 mg Pap. 2 mg Hy. 0.04 mg	—	—	130	140	120
	133	5	M	Herniorraphy	Trimep. 30 mg Pap. 5 mg Hy. 0.1 mg	—	—	100	140	95
Rates 120 beat min^{-1} or less but increase in rate > 40 beat min^{-1}	7	16	M	Pyeloplasty	Pap. 15 mg Hy. 0.3 mg	Fazadinium	0.2 mg	75	120	90
	27	39	F	Cholecystectomy	Pap. 15 mg Hy. 0.3 mg	Fazadinium	—	65	110	75
	32*	62	F	Colostomy	Pap. 15 mg Atropine 0.6 mg	Atracurium	—	70	120	75

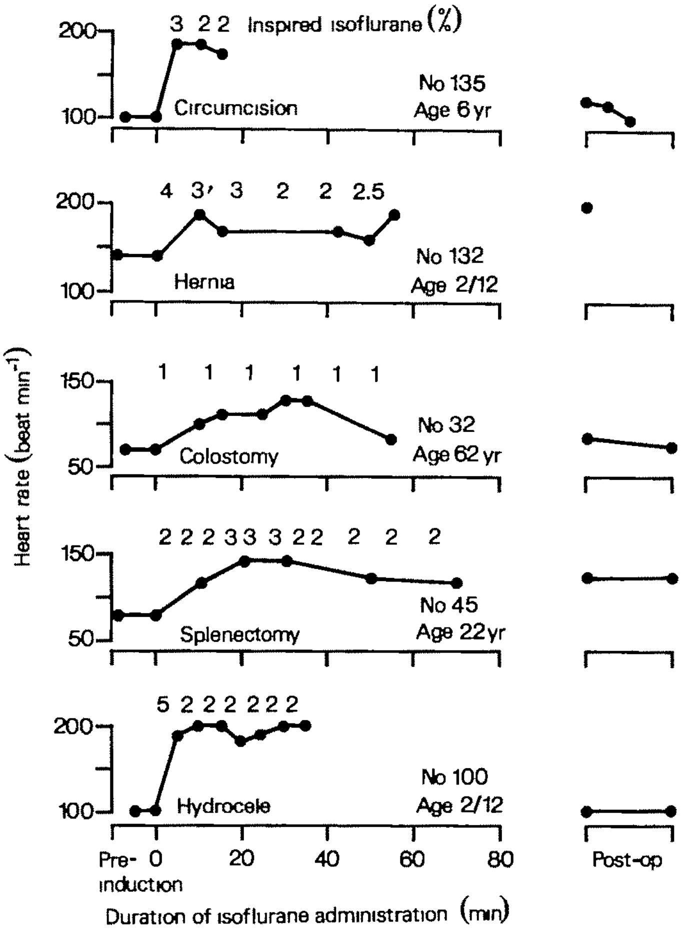

FIG. 4. Heart rates in five patients showing tachycardia apparently related to anaesthesia (patients who received fazadinium are excluded).

trolled with 2% isoflurane and required phentolamine 0.5 mg once during and once after the end of the operation. The arterial pressure remained greater than 180 mm Hg systolic for 2 h in the period after operation. In patient No. 119, the arterial pressure increased from a pre-induction value of 140/80 mm Hg to 170/100 mm Hg, but this was easily controlled by increasing the inspired concentration of isoflurane from 1 to 2%. In those patients breathing spontaneously, it was possible to maintain an adequate depth of anaesthesia without the systolic arterial pressure decreasing to less than the values shown in table XI.

Cardiac rhythm

One hundred and one of the 110 monitored patients remained in sinus rhythm throughout surgery. Three patients had atrial fibrillation before surgery and this continued unchanged during the anaesthetic. Another patient had pre-existing atrial extrasystoles and these also continued during surgery. Changes in rhythm occurred in five patients (table XII) in whom no abnormalities in rhythm were observed before surgery. Quite large doses of adrenaline were used in three of these patients, one of whom developed ventricular extrasystoles (1 min^{-1}) while two developed periods of nodal rhythm. Patient No. 9 developed fibrillation/flutter at the end of the anaesthetic but the same abnormality of rhythm occurred in two subsequent anaesthetics for repeat cystoscopy, halothane being the main agent for one and enflurane for the other. On each occasion the patient reverted to normal sinus rhythm early in the period after operation. Substantial doses of adrenaline were administered to 19 patients in addition to those listed in table XII,

TABLE XI. *Minimum systolic arterial pressure in patients breathing spontaneously*

AP (mm Hg)	No. patients
60	1
70	1
80	12
90	14
100	11
110	12
120	9
130	6
140	5
150	2

without development of any abnormality of cardiac rhythm (table VII).

Dose requirement of neuromuscular blocking drugs.

Table VI shows the doses which were required to maintain adequate surgical relaxation. The doses of atracurium and vecuronium are plotted against the duration of the period of the operation requiring relaxation (fig. 6). All patients receiving pancuronium, fazadinium, alcuronium and vecuronium required neostigmine 2.5–5 mg to give a sustained tetanus at the end of surgery. However, in eight of the 14 patients receiving atracurium, neuromuscular conduction appeared adequate and neostigmine was not used. They are shown as open circles in figure 6, and the requirement for neostigmine did not appear to depend upon the dose in relation to duration of operation.

Difficulty was encountered in reversing neuromuscular blockade in one patient weighing 78 kg (No. 11) who received alcuronium 20 + 10 mg in the course of a pyelolithotomy lasting 90 min. It was not possible to obtain a sustained tetanus following the administration of neostigmine 5 mg at the end of operation and anaesthesia was maintained with nitrous oxide for a further 1 h, after which there was a good response to an additional neostigmine 2.5 mg. Inspired isoflurane concentration was 1% until 20 min before the end of operation, when it was reduced to 0.5%.

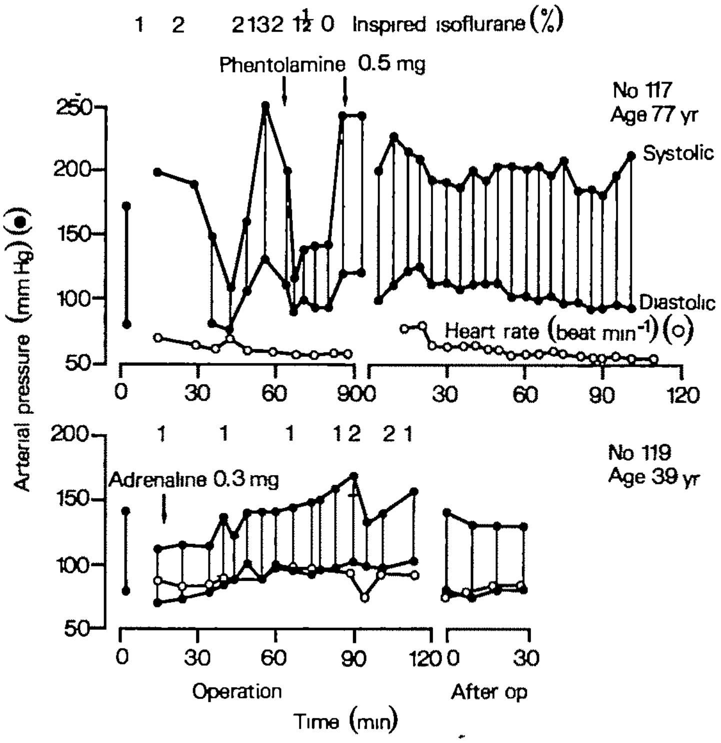

FIG. 5. Arterial pressure in two patients showing hypertension during anaesthesia. Patient No. 117 was undergoing mastectomy and No. 119 removal of a parathyroid adenoma.

TABLE XII. *Patients who developed abnormal rhythms during anaesthesia and surgery. No patients had arrhythmia or any condition predisposing to arrhythmia before surgery*

Serial No.	Age (yr)	Operation	Adrenaline (mg)	Cardiac rhythm
1	57	Parathyroidectomy	0.25 (74.5 kg)	Monofocal ventricular extrasystoles 1 min^{-1} throughout surgery.
9	78	Transurethral resection of bladder tumour	nil	Abrupt onset of fibrillation/flutter at end of operation (duration 20 min). Arrhythmia continued for 2 h into the period after operation and responded to lanoxin 0.25 mg i.v.
13	54	Cholecystectomy	nil	10-min period of nodal rhythm starting 40 min after induction.
72	63	Parathyroidectomy (66	0.35 (66 kg)	Several episodes of nodal rhythm.
113	73	Nephrectomy	0.3 (70 kg)	Three episodes of nodal rhythm lasting about 20 min.

Untoward events

Generally, the course of anaesthesia was uneventful. One patient coughed unexpectedly during a transurethral resection of prostate after breathing 3% isoflurane for 5 min and 1.5% isoflurane for a further 10 min. A child of 5 months who had not received premedication had troublesome secretions during anaesthesia, but these responded rapidly to the administration of atropine 0.2 mg. The most difficult problem arose in two children aged respectively 2 and 4 months, who had intermittent periods of apnoea during anaesthesia. In each case the inspired concentration of isoflurane was in the range 1.5–3%. Respiration was not obstructed and anaesthesia appeared to be neither too deep nor too light. Neither child responded to surgical stimulation, and the lungs of both were ventilated by manual compression of the reservoir bag. At the end of surgery, when the inspired isoflurane concentration was reduced to zero, normal breathing rapidly returned and each child awoke while still on the operating table.

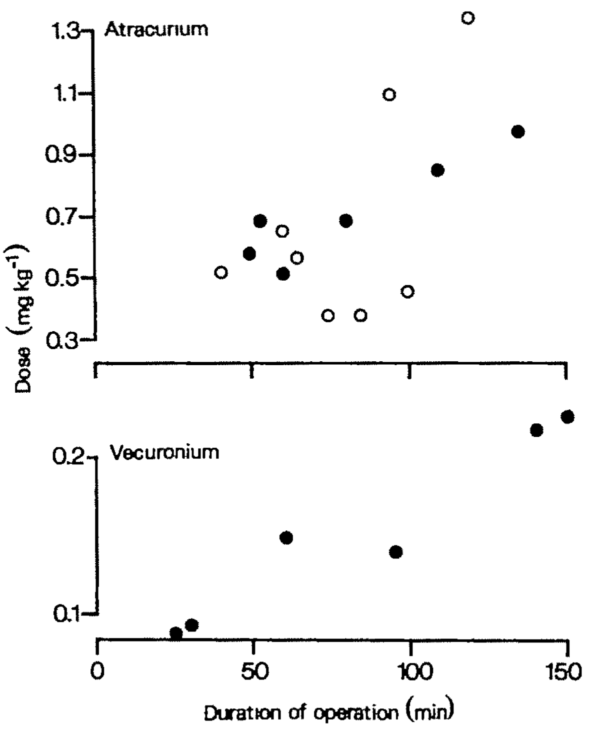

FIG. 6. Dosage of atracurium and vecuronium as a function of duration of anaesthesia. ● = Neostigmine required; ○ = neostigmine not required.

In the early period after operation, five patients vomited. Three shivered for a few minutes, one was restless and another was confused and disorientated for the first 1 h. The most difficult problems in the period after operation were two patients who became delirious. Each had to be restrained for several minutes, and they did not respond to morphine i.v.

Consumption of isoflurane

On average 22 ml of liquid isoflurane was administered per patient. The patients comprised 80 who breathed spontaneously with a median inspired concentration of 2% and a mean duration of 32 min, and a further 55 who were ventilated artificially with a median inspired concentration of 1% and a mean duration of 87 min. Fresh gas flow ranged from 6 to 9 litre min^{-1}.

Effect of exhaustion of isoflurane in the vaporizer

At a flow rate of carrier gas 6 litre min^{-1} the vaporizer, set to a nominal concentration of 3%, actually delivered 2.8% isoflurane. From the time the level of isoflurane formed a diameter across the lower port of the sight glass until it formed a tangent to the bottom of the port took about 20 min, during which the concentration decreased from 2.8 to 2.7%. Thereafter, the delivered concentration decreased precipitously to less than 1% in 6 min (fig. 7A).

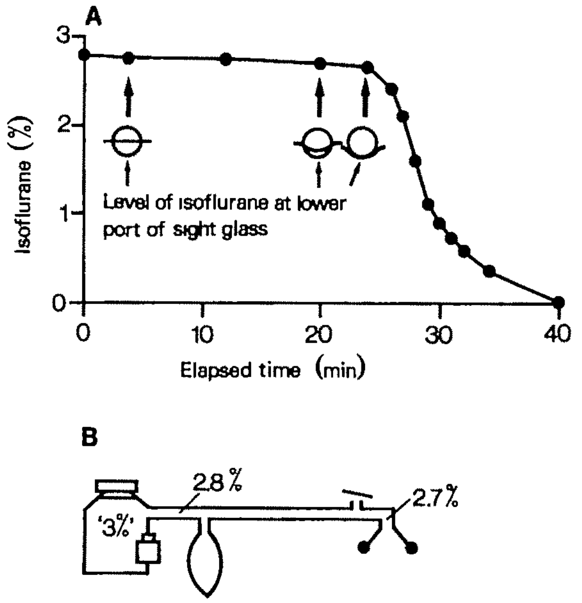

FIG. 7. A: Concentration of isoflurane delivered from a Cyprane vaporizer, plotted as a function of time, immediately before and after the level of liquid reaches the bottom of the lower port of the sight glass. Carrier gas flow rate 6 litre min^{-1}. B. Concentration gradient of isoflurane vapour in a Magill system at a fresh gas flow rate of 6 litre min^{-1}. Carrier gas flow rate 6 litre min^{-1}.

Concentration gradients within the gas circuit

With a standard Magill system, the concentration of isoflurane delivered to the patient was 2.7% when the concentration leaving the vaporizer was 2.8% (fig. 7B). The mixture had been passing through the circuit for 30 min before the measurements were made. The flexible parts of the circuit were made of black conductive rubber.

DISCUSSION

The authur made an abrupt transition to the exclusive use of isoflurane for this series of 135 patients, without any previous practical experience of the agent. While this presented no major difficulty, there was a definite learning curve and the quality of anaesthesia improved as experience was increased. No clear contraindications to the use of isoflurane have been reported and none emerged in this study, in relation to either the type of surgery or pre-existing disease.

Induction

For all the adult patients, anaesthesia was induced with thiopentone. Immediately thereafter all patients tolerated an inspired concentration of 2% isoflurane without coughing. However, without thiopentone, 2% isoflurane was found to be irritant, imparting a distinctive burning sensation in the back of the nose. Therefore, when thiopentone was not used, it was necessary to commence with 1% isoflurane although this could be increased to 2% after a few breaths. This contrasts with halothane, which can be breathed at 2% concentration by the conscious patient. Thus, halothane is initially tolerable at 2.6 MAC multiples and isoflurane at only 0.8 MAC multiples. Therefore, in spite of the lower blood solubility of the latter, induction was proved to be no quicker than with halothane (Pandit, Leach and Steude, 1983).

In the case of small children, induction was by isoflurane vaporized in oxygen to avoid the cerebral arousal caused by nitrous oxide. Nitrous oxide was introduced to the mixture after the child had lost consciousness. With the inspired concentration of isoflurane increasing according to the schedule outlined above, loss of consciousness usually occurred within 1 min and always within 90 s, although the mask was initially held clear of the face for approximately 20–30 s.

Maintenance of anaesthesia

During the maintenance of anaesthesia without neuromuscular blockade, the mean of the maximal inspired concentration required was 2.3% which, after about 1 h of anaesthesia, would result in an alveolar concentration of about 1.6% (Cromwell et al., 1971) or 1.2 MAC multiples. Allowing an additional 0.6 MAC multiples for the use of 65% nitrous oxide, the total would be of the order of 2.2 MAC multiples, which is a reasonable value to secure freedom from response to maximal surgical stimulus in the great majority of patients. In fact, only one patient responded overtly to surgical stimulation by coughing, on one occasion in this study. In patients receiving neuromuscular blocking drugs the inspired concentration was much more constant—with a mean value of 1.1%.

Homi and his colleagues (1972) reported inspired concentrations of isoflurane in the range 1.2–2.5% during maintenance of anaesthesia with a 50% nitrous oxide in oxygen mixture as carrier gas.

Values in the present study cannot easily be compared with those reported in the North American Multicentre trial (Cahalan, 1982), in which no distinction was made in reporting concentrations for patients with and without neuromuscular blockade. Furthermore, reported concentrations were those delivered into the system and were not necessarily the same as the inspired concentration, since rebreathing circle systems with soda-lime were generally used, and the fresh gas flow rate was not specified. Nevertheless, during the maintenance of anaesthesia the mean value for the highest concentration of isoflurane delivered to the gas circuit was 1.7% and for the average concentration was 1.2% (Cahalan, 1982). The range of delivered concentrations was 0.4–3.2%, which seems to be in general accord with the present study.

Recovery

Although the mildly irritant smell of isoflurane delays the rapidity of induction, recovery is determined predominantly by the low solubility of the agent in body fluids and is, therefore, very rapid. The wash-out curves (fig. 1) relate to adults ventilated artificially at 6 litre min^{-1} after 1 h of equilibration with 1% isoflurane and cannot, therefore, be compared directly with the data of Cromwell and colleagues (1971), who studied the elimination of sub-anaesthetic concentrations of isoflurane in volunteers breathing spontaneously. Nevertheless, in that study, alveolar partial pressure reached 37% of the initial arterial tension at the end of the first minute of wash-out after 64 min inhalation of 0.25% isoflurane, a time-course which is compatible with our own data.

The quality of recovery was remarkably good and the incidence of nausea, vomiting, shivering and distress was minimal, and decreased with experience. The only major problem was delirium, which occurred in two patients, requiring restraint by more than one nurse and not responding to morphine i.v. Homi and his colleagues (1972) reported postoperative excitement and delirium in 6% of their patients, while Pauca and Dripps (1973) observed mild excitement in 12% and moderate excitement in 3% of their patients. Emergence delirium occurred in 3.2% of patients reported in the *American New Drug Application for Isoflurane* (p.642), although the incidence after halothane was not significantly different. Emergence delirium was also noted by White (personal communication) during a study of totally closed circuit isoflurane anaesthesia without the use of nitrous oxide or opiates. I concur with the view of Pauca and Dripps (1973) that the condition is caused by sudden perception of postoperative pain as a result of the rapid wash-out of isoflurane. The condition is seen at its worst after painful procedures (e.g. upper abdominal or renal surgery) in which regional anaesthesia or opiates have not been used. In the present series, the two cases of delirium occurred early in the series. Patient No. 14 had undergone a vagotomy and pyloroplasty, and patient No. 15 an excision of parotid tumour, neither having received regional anaesthesia or opiate before recovery. Thereafter, this complication appeared to be avoided in potential cases by the use of either regional anaesthesia or an opiate before recovery commenced. This problem might well be encountered during the early exploratory use of isoflurane, when the use of regional anaesthesia and opiates are minimized to facilitate observations of the effects of isoflurane itself.

Heart rate

Early clinical experience drew attention to the increase in heart rate (Homi et al., 1972; Pauca and Dripps, 1973). The Multicentre Trial (Forrest, 1982) reported a mean heart rate of 87.71 beat min^{-1} before induction, which may be compared with 78.4 beat min^{-1} in the present series. They reported a mean "typical" heart rate of 89.99 beat min^{-1} during maintenance of anaesthesia, which may be compared with the time weighted mean of 83.3 beat min^{-1} reported here. The standard error of the mean "typical" heart rate in the Multicentre Trial was 0.29, corresponding to a standard deviation of 22.26 in a study of 6798 patients. Assuming normal distribution, this would indicate a 95% range extending up to 149.63 beat min^{-1}. As in the present series, the Multicentre Trial found the "typical" heart rate during anaesthesia to be markedly age-dependent. For patients younger than 1 yr, the mean was 149.9 (SD 19.5) beat min^{-1}, indicating a 95% range extending to about 190 beat min^{-1}, which may be compared with a mean of 159 (SD 30) beat min^{-1} for the small number of patients younger than 1 yr in the present study.

The Multicentre Trial reported a mean value for the maximal heart rate during anaesthesia of 101.81 (SD 23.9) beat min^{-1}, which may be compared with the values in figure 3. The Multicentre Trial does not report age-dependence of the fastest heart rate during maintenance, but this is clearly shown in figure 3.

Figure 4 shows no clear relationship between inspired concentration of isoflurane and the heart rate, although the tachycardia does seem to be related to the duration of anaesthesia. In reporting the present series, it seemed useful to identify those patients in whom there was either a maximal heart rate of more than 120 beat min^{-1} or an increase of more than 40 beat min^{-1} compared with the value before induction (table X). Four of seven patients who received fazadinium fell into one of these categories. Since fazadinium has now been withdrawn from clinical use, this observation is of theoretical interest only. Eight of the remaining 10 patients in table X were children, and in five of these the heart rate was within the upper limit of normal (Davenport, 1980). There remain five patients exhibiting appreciable tachycardia (fig. 4). None had any appreciable blood loss or pyrexia and none gave any cause for anxiety apart from the tachycardia which was not treated.

In most instances, tachycardia occurred in young patients in whom there was no cause for concern about increased myocardial work resulting from the increased rate–pressure product. The ST segment remained unchanged in all monitored patients using the CM 5 lead configuration. This also applied to the 17 patients who had pre-existing myocardial ischaemia or angina.

Figure 2 shows an inverse relationship between mean heart rate before induction and the change in heart rate of each group following induction. This relationship is significant ($P < 0.01$).

The slowest heart rates recorded were 40 beat min^{-1} in two patients and 45 beat min^{-1} in another three patients.

Arterial pressure

Isoflurane is a potent hypotensive agent, an effect achieved predominantly by a reduction in systemic vascular resistance rather than by a decrease in cardiac output (Eger, 1981). Thus, its effect resembles, in some respects, that of sodium nitroprusside. In the present study, the ability to maintain an adequate depth of anaesthesia was never compromised by hypotension to less than the values shown in table XI, which were considered acceptable in a supine patient with no clinical indication of defective peripheral circulation. It was generally very easy to control an increasing arterial pressure with isoflurane, but an exception was patient 117 (fig. 5). This patient was in normal health before and after operation and there was nothing to suggest the possibility of a phaeochromocytoma.

Cardiac rhythm

An outstanding feature of isoflurane in the present series was the stability of the cardiac rhythm. Patient No. 1 exhibited one monofocal ventricular extrasystole per minute following administration of adrenaline (table XII). Two other patients developed episodes of nodal rhythm after adrenaline, and this change was also observed by Johnston, Eger and Wilson (1976). Otherwise, the substantial doses of adrenaline recorded in table VII were without effect. Johnston, Eger and Wilson (1976) found the ED_{50} of adrenaline for initiation of ventricular extrasystoles during isoflurane anaesthesia to be 6.72 (SD 0.66) μg/kg body weight. One of their patients developed arrhythmia after a dose of 5.5 μg kg^{-1}, which was the largest dose used in the present series. The minimal response to the dose range of adrenaline in the present study supports Johnston's evidence for its safety. The fact that patient No. 9 developed fibrillation/flutter at the end of three consecutive anaesthetics, all with different agents, suggests that he was responding to the general stress of anaesthesia and surgery rather than to any particular anaesthetic agent.

Respiration

British anaesthetic practice has long differed from that of the United States in its tolerance of unassisted spontaneous respiration for a wide range of surgical procedures not requiring the use of a neuromuscular blocking drug. With halothane as the main anaesthetic agent, minute volumes of respiration may decrease to as low as 2.3 litre min^{-1} with arterial P_{CO_2} increasing to 9 kPa, but without demonstrable harm to the patient (Nunn and Hill, 1960; Nunn, 1964).

In volunteers, anaesthetized with isoflurane without surgical stimulation, there is evidence that isoflurane is a more powerful respiratory depressant than halothane (Fourcade et al., 1971). However, the addition of nitrous oxide and surgical stimulation greatly reduces the hypercapnia resulting from the use of isoflurane (Eger, 1981). It would be difficult to predict the degree of respiratory depression under the conditions of the present series. However, there was no clinical evidence of any greater respiratory depression than is normally seen with halothane under similar conditions. In patient No. 66, spontaneous respiration was maintained during a mastopexy lasting for 165 min. In view of the duration of operation, arterial $P\text{CO}_2$ was measured at the end of operation and was 7.9 kPa, which is within the range encountered by the author under similar circumstances using halothane (Nunn, 1964).

Relaxation

No attempt was made to achieve surgical relaxation with isoflurane in the present series. In the 55 patients who were ventilated artificially, tracheal intubation was achieved, not with suxamethonium, but with one of the first five neuromuscular blocking drugs listed in table VI. The initial dose of the neuromuscular blocker was calculated to provide sufficient relaxation for intubation at a time when the alveolar concentration of isoflurane was low. Therefore, it was not possible to make any assessment of potentiation of neuromuscular block by isoflurane. However, repeat dosage of the long acting drugs, pancuronium, fazadinium and alcuronium, was only required in five patients, in spite of the duration of operation which greatly exceeded the normal duration of action of the drugs concerned. Peritoneal closure never required a supplementary dose of the neuromuscular blocker, and it seems likely that this was the result of potentiation by isoflurane, usually at an inspired concentration of 1%. Reversal with neostigmine was always used and presented no difficulty except in patient No. 11 referred to above. Dosage of the short acting drugs atracurium and vecuronium gave no obvious indication of any potentiation by isoflurane (fig. 6). Dosage of atracurium appears similar to the range of 0.005–0.01 mg kg^{-1} min^{-1} reported by Flynn and colleagues (1983) in patients not receiving a volatile anaesthetic.

Anaesthetic apparatus

Isoflurane has a lower solubility in conductive rubber tubing than have other volatile agents (Eger, 1981), the solubility coefficient being only one-tenth that of methoxyflurane. Figure 7B shows the negligible loss of concentration during transit through a conventional Magill system.

The accuracy of the vaporizer available to us was within 10% of nominal delivered concentration and was adequate for clinical use. It was, however, startling to observe the rapidity of decrease in delivered concentration once the fluid level had fallen below the lower rim of the lower port of the sight glass (fig. 7A). Taken in conjunction with the very rapid washout of alveolar isoflurane (fig. 1), it is clear that the utmost vigilance must be exercised to be certain that the vaporizer never becomes empty during use.

CONCLUSIONS

The present study indicates that isoflurane is a very satisfactory anaesthetic agent which is applicable to a wide range of surgery. It would appear to have important advantages, particularly since so many favourable qualities appear to be combined in the one agent.

Minor disadvantages include the mildly irritant nature of the vapour, which demands some skill and experience to achieve the best results during an inhalation induction and also slightly limits the speed of induction. The occasional case of tachycardia may cause some concern and wider experience will be needed to assess its importance in the clinical environment. It appears that emergence delirium can be avoided by appropriate care to prevent the sudden appreciation of pain on awakening from anaesthesia.

It is unlikely that anyone will overlook the fact that isoflurane is considerably more expensive than enflurane and very much more expensive than halothane. The mean utilization of liquid isoflurane 22 ml per patient in this study accords with the high fresh gas flow rates and the delivered concentrations. Essentially non-rebreathing systems were used so that the inspired concentration of isoflurane should be known. However, substantial economies could be achieved by reduction in fresh gas flow rates or by the use of closed circuit anaesthesia (O'Callaghan et al., 1983).

There is, of course, a learning curve in the use of any new technique or drug. Isoflurane is no exception and results in the present series improved with experience. Thus 10 of the postoperative complications mentioned above were encountered in the first 50 patients and only two in the following 85 patients.

Although this and other studies have shown that isoflurane is generally a very satisfactory agent, there is now a need for comparative studies with other volatile agents in the clinical environment. This study, those of Dobkin and colleagues (1971), Homi and co-workers (1972), Pauca and Dripps (1973) and the Multicentre Trial have not attempted to make a controlled comparison of isoflurane with other volatile agents in the context of routine surgery. This should now be undertaken.

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CARDIAC RATE AND RHYTHM DURING ANAESTHESIA FOR DENTAL EXTRACTION

A comparison of Halothane, Enflurane and Isoflurane

W. R. CASSON AND R. M. JONES

SUMMARY

Cardiac rate and rhythm were compared in 60 patients having dental extractions under conventional general anaesthesia using halothane, enflurane or isoflurane to supplement nitrous oxide in oxygen. The incidence of arrhythmia was higher in the halothane group when compared with both the enflurane ($P < 0.05$) and the isoflurane ($P < 0.05$) groups. Heart rates, measured at 1-min intervals, tended to be more rapid in the isoflurane group compared with the other two groups ($P < 0.001$ in both instances), and patients anaesthetized with enflurane tended to have more rapid heart rates than those anaesthetized with halothane ($P < 0.001$).

The occurrence of cardiac arrhythmia during dental extraction under local or general anaesthesia is well documented (Kaufman, 1965, 1966; Hughes et al., 1966; Tuohy, 1968; Rollason and Dundas, 1970; Ryder, 1970). Although the aetiology of these disturbances of rhythm has not been fully elucidated, they are thought to result from an increase in cardiac sympathetic nervous activity, in response to surgical stimulation (Plowman, Thomas and Thurlow, 1974; Alexander and Murtagh, 1979). When compared with halothane-supplemented anaesthesia, the administration of enflurane is associated with less arrhythmia during dental extraction (Wright, 1980), and isoflurane-supplemented anaesthesia is known to be associated with greater stability of rhythm after the injection of adrenaline (Johnston, Eger and Wilson, 1976). We have studied the incidence of cardiac arrhythmia, and compared heart rates, during nitrous oxide in oxygen anaesthesia supplemented with halothane, enflurane or isoflurane.

PATIENTS AND METHODS

Sixty unpremedicated adults (ASA Grade I), scheduled to have dental extractions under general anaesthesia as out-patients, were allocated randomly to three groups to receive halothane, enflurane or isoflurane. Patients were excluded from the study if they were receiving concurrent drug therapy, if they had a history of cardiovascular disease, if they had any cardiac arrhythmia, or if they had a heart rate greater than 120 beat min^{-1} or less than 60 beat min^{-1} before the induction of anaesthesia. The age, weight and sex distribution, and operating times were similar in the three groups (table I).

TABLE I. *Age, sex and weight characteristics, and operating times. Data expressed as mean (SD) where applicable*

	Halothane	Enflurane	Isoflurane
n	20	20	20
Male	4	4	8
Female	16	16	12
Age (yr)	26.30(8.25)	22.65(6.01)	25.55(6.11)
Range	18–53	19–44	18–45
Weight (kg)	62.48(12.46)	62.40(11.03)	63.05(11.15)
Range	48–99	44–88	48–80
Operating time (min)	17.15(8.71)	14.35(6.11)	19.30(9.92)
Range	7–44	6–29	8–45

Once the patient was settled on the operating table, an ECG monitor (5-lead) (Physio-Control Lifepak 6) was connected to the patient, and the cuff of an automatic non-invasive arterial pressure and pulse monitor (Dinamap) positioned on the right arm. After baseline recordings had been obtained a 23-gauge needle was inserted to a vein on the dorsum

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of the left hand, and anaesthesia induced with a dose of thiopentone sufficient to abolish the eyelash reflex. Suxamethonium 1 mg kg^{-1} was administered to facilitate the passage of a nasotracheal tube and a throat pack was placed in position. Maintenance of anaesthesia was with 66% nitrous oxide and halothane, enflurane or isoflurane (using a recently calibrated, temperature-compensated vaporizer (Fluotec Mark 3, Enfluratec or Fortec, respectively—Cyprane Ltd)) in oxygen, the concentration of the volatile agent being adjusted to give suitable operating conditions (using an inspired concentration between 1% and 3%). A Bain type co-axial breathing system was used, delivering a fresh gas flow sufficient to minimize rebreathing during spontaneous ventilation. Surgery commenced once normal sinus rhythm had been established. The end-tidal carbon dioxide concentration was measured with an infra-red analyser (Hewlett–Packard 47210 Capnometer with 14369A transducer). The electrocardiogram (Standard Lead 2) was displayed continuously until the end of surgery and a record obtained of any rhythm disturbance occurring in response to surgical stimulation. Arterial pressure and heart rate were measured and recorded at 1-min intervals.

TABLE II. *Incidence of arrhythmias. *Ventricular ectopics or supraventricular ectopics with aberrant conduction*

	Halothane	Enflurane	Isoflurane
Ventricular ectopics	2	0	0
Coupled beats*	2	0	0
Multifocal ectopics	1	0	0
Superventricular ectopics only	0	0	1
Nodal rhythm	1	0	0
No arrhythmias	14	20	19

RESULTS

Results are reported as mean (SD) as applicable. Statistical analysis utilized Fisher's exact probability test or Student's *t* test as appropriate. There were no significant differences in end-tidal carbon dioxide concentration between the three groups; $P\mathrm{E}_{\mathrm{CO}_2}$ did not exceed 6.6 kPa in any patient. The incidences of arrhythmia observed and recorded are shown in table II. The high incidence of arrhythmias (30%) during dental extractions in patients receiving halothane was confirmed: examples are shown in figure 1. Interpretation of this type of arrhythmia is

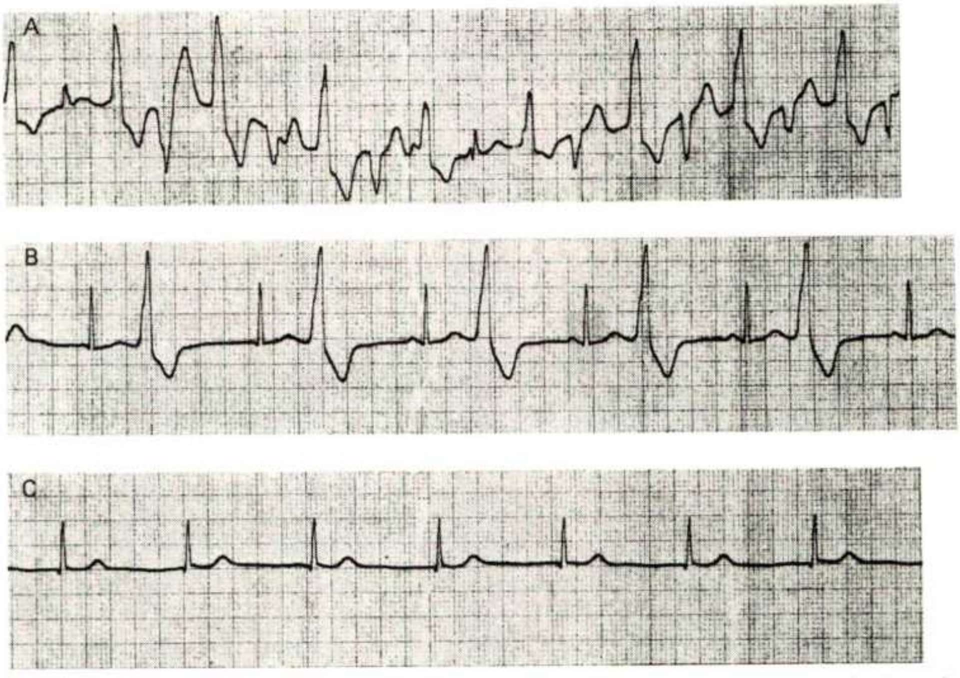

FIG. 1. Arrythmias recorded in patients anaesthetized with halothane. A: Female 18 yr. Multifocal ectopic beats recorded during the extraction of a 3rd molar tooth. B: Female, aged 24 yr. Coupled beats recorded during extraction of a 3rd molar tooth. C: Female, aged 24 yr. Nodal rhythm recorded during extraction of a 3rd molar tooth.

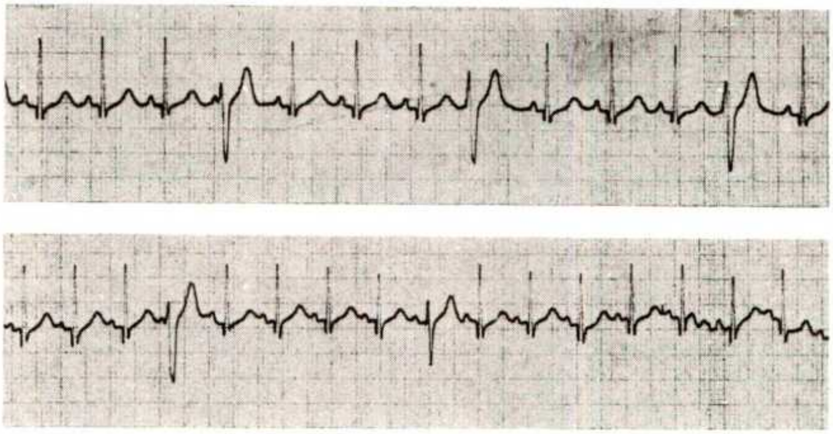

FIG. 2. Arrhythmia recorded in a patient anaesthetized with isoflurane. Male aged 28 yr. Supraventricular ectopic beats recorded during extraction of a 3rd molar tooth.

difficult, particularly the differentiation between supraventricular ectopic beats with aberrant conduction and ectopic beats of ventricular origin (Sandler and Marriot, 1965). A diagnosis of ventricular ectopics was made only if the added beat was immediately followed by either a P wave (that is, there was retrograde conduction from the ventricle) or by a definite compensatory pause. In the halothane group, four patients had coupled beats (in two patients these were of ventricular origin) and one patient had multi-focal ectopic beats at least some of which were of ventricular origin (fig. 1). Only one patient in the isoflurane group had any type of disturbance of rhythm, an occasional supraventricular ectopic beat (fig. 2). There were no arrhythmias observed in the enflurane group. Statistical analysis revealed a significantly higher incidence of arrhythmia in the halothane group compared with the isoflurane ($P < 0.05$) and the enflurane ($P < 0.05$) groups.

The heart rates observed and recorded varied considerably depending on the degree of surgical stimulation. Therefore, we felt that the most meaningful comparison would be made between the groups by comparing the mean heart rates in the three groups and then comparing all the individual readings. There were significant differences between the three groups: heart rates in the isoflurane group (range of means, 74–116 beat min^{-1}; overall mean, 101 beat min^{-1}; SD 17.8) were significantly higher than in both the enflurane ($P < 0.001$) and the halothane groups. Patients in the enflurane group (range of means, 75–112 beat min^{-1}; overall mean, 95 beat min^{-1}; SD 14.8) had significantly faster ($P < 0.001$) heart rates than those in the halothane group (range of means, 72–97 beat min^{-1}; overall mean, 82 beat min^{-1}; SD 15.9). This is represented graphically in figure 3, where the number of observations of a certain heart rate is plotted against that rate. This also demonstrates that the heart rates recorded in the patients receiving halothane showed less variability when compared with the two other groups.

DISCUSSION

A number of factors contribute to the disturbances of cardiac rhythm which may occur during oral surgery. These include hypoxia, hypercarbia and increased sympatho–adrenal activity (Tuohy, 1968). Their incidence is decreased by prior infiltration of the operation site with lignocaine (Kaufman, 1965) and by beta-adrenergic antagonists both with (Tolas and Allen, 1970) and without (Rollason and Hall, 1973; Rollason and Russell, 1980) membrane stabilizing activity. Similar disturbances of rhythm have been observed by neuroanaesthetists on manipulation of the fifth cranial nerve during surgery for trigeminal neuralgia (Ballantine and Jackson, 1960; Hunter, 1975). These observations would suggest that increased sympathetic nervous activity or increased release of catecholamines from the adrenal glands, or both, in response to surgical stimulation are involved in the genesis of these arrhythmias. It

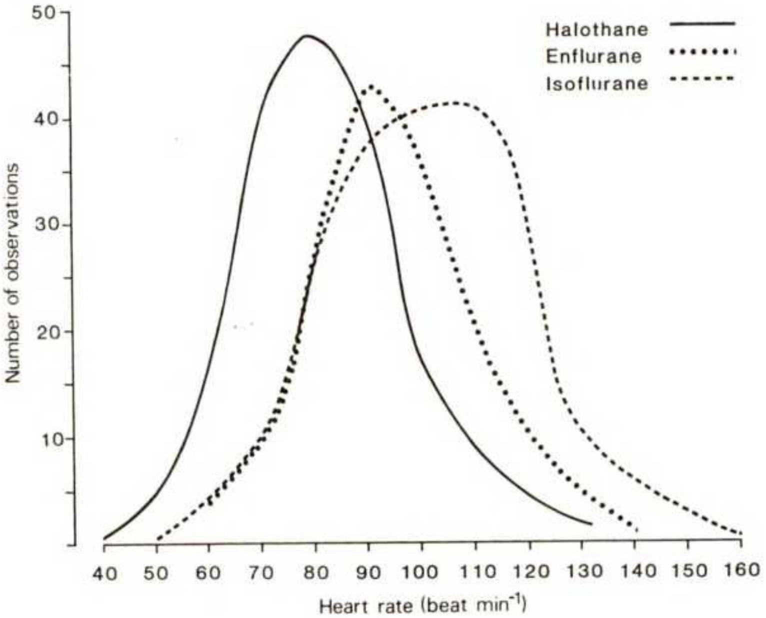

FIG. 3. Comparison of heart rates.

has also been suggested that there is a concurrent increase in parasympathetic activity (Taggart et al., 1976). The incidence of cardiac arrhythmia during general anaesthesia for dental extractions is increased by the administration of atropine (Thurlow, 1972) and when halothane, as opposed to enflurane, is used to supplement nitrous oxide in oxygen anaesthesia (Wright, 1980). None of the patients in our study received an anti-cholinergic agent, none reached an end-tidal carbon dioxide concentration near the so called "arrhythmic threshold" (Black et al., 1959) and all patients breathed 30% oxygen via an endotracheal tube. Although halothane itself has been reported to be associated with an increase in circulating noradrenaline (Joyce et al., 1982) this does not occur after the i.v. induction of anaesthesia (Joyce, Roizen and Eger, 1981). The injected dose of adrenaline which is required to produce ventricular extrasystoles is known to be reduced during halothane anaesthesia compared with both enflurane and isoflurane anaesthesia (Reisner and Lippmann, 1975; Johnston, Eger and Wilson, 1976). Thus, if the cause of arrhythmia during general anaesthesia for oral surgery is indeed an increase in sympatho–adrenal activity, one would expect the incidence to increase during halothane anaesthesia.

Cardiac arrhythmias result from an alteration in automaticity or re-entry of the cardiac impulse. Pratila and Pratilas (1978) have emphasized that the sensitization of the heart to catecholamines which leads to the occurrence of arrhythmias has, as an underlying mechanism, re-entry of the cardiac impulse. The likelihood of re-entry occurring is increased in any situation where there is slowing of conduction resulting in temporary uni-directional block (Jones, Broadbent and Adams, 1984). Of the three volatile agents used in this study, halothane causes more slowing of A–V nodal and His–Purkinje conduction than the other two and appears to be the only one to cause slowing of ventricular conduction (Atlee and Peterson, 1982). Indeed, isoflurane causes the least slowing of A–V nodal conduction and has little or no effect on His–Purkinje conduction. Thus, as Jones (1984a) has noted previously, the conditions for a re-entry arrhythmia are more likely to occur during halothane, as distinct from enflurane and isoflurane, anaesthesia. Our study has confirmed the high incidence (30%) of arrhythmia during dental extractions when halothane is used.

As it appears that ventricular fibre conduction is minimally affected by either enflurane or isoflurane, premature ventricular contractions would be equally unlikely to occur during enflurane and isoflurane anaesthesia. Our study has confirmed this electrophysiologically-based prediction (the only disturbance of sinus rhythm recorded being an occasional supraventricular ectopic beat in one patient anaesthetized with isoflurane).

The occurrence of a tachycardia during isoflurane anaesthesia has been noted previously (Skovsted and Sapthavichaikul, 1977); this is associated with a decrease in systemic vascular resistance, a decrease in stroke volume and maintenance of cardiac output (Stevens et al., 1971). Two factors may contribute to the tachycardia associated with isoflurane anaesthesia (Jones, 1984b): first, systemic vascular resistance is markedly decreased, and second, baroreflex activity remains relatively intact except at deeper levels of isoflurane anaesthesia (Skovsted and Sapthavichaikul, 1977; Seagard et al., 1983; Kotrly et al., 1984). Therefore, one might expect that patients anaesthetized with isoflurane would have a more rapid heart rate than patients anaesthetized with enflurane or halothane, both of which cause significant depression of baroreflexes (Duke, Fownes and Wade, 1977; Morton, Duke and Ong, 1980). One might expect halothane anaesthesia to be associated with the lowest mean heart rate, since there is a suggestion that this agent causes the most significant slowing of S–A node discharge (Merlos et al., 1980). In addition, enflurane might be expected to be associated with an intermediate range of heart rates, since this agent causes less slowing of S–A node discharge than halothane and also significantly depresses baroreflexes. In our study the comparison of heart rates confirmed these expectations.

In summary, both enflurane and isoflurane have been shown to be associated with less cardiac arrhythmia than halothane when used to supplement nitrous oxide in oxygen anaesthesia for dental extractions. Isoflurane was associated with a higher heart rate than the other two agents, and enflurane with a more rapid rate than halothane. Isoflurane may be the agent of choice when enflurane is relatively contraindicated, for instance in patients with epilepsy (Linde et al., 1970).

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MATERNAL AND NEONATAL RESPONSES RELATED TO THE VOLATILE AGENT USED TO MAINTAIN ANAESTHESIA AT CAESAREAN SECTION

J. S. CRAWFORD, M. LEWIS AND P. DAVIES

SUMMARY

A standardized technique of general anaesthesia, with one randomly selected variable, was provided for 237 patients undergoing elective and 540 undergoing emergency Caesarean section. The variable was the volatile agent used to maintain anaesthesia, the choice resting between trichloroethylene (0.2 or 0.3 vol.%) and halothane (0.2, 0.3, 0.4 or 0.5 vol.%). No association was found between the type of agent and the duration of anaesthesia, or the duration of either the I–D or the U–D interval. A smaller total dose of suxamethonium was administered in conjunction with the higher concentrations of volatile agent. A statistically significant but clinically unimportant increase in the time elapsing from the cessation of anaesthesia to maternal achievement of a "safe level of consciousness" was found with the higher concentrations. The incidence of maternal awareness plus unpleasant dreams was unacceptably high when the lower concentrations were used, and it is recommended that either trichloroethylene 0.3 vol.% or halothane 0.4 or 0.5 vol.% be used. Neither agent, at these concentrations, was associated with neonatal depression in group A elective sections in which the fetus presented by the vertex, and although there was a possible tendency for their use in cases of fetal compromise to be associated with an increase in the incidence of neonatal respiratory depression, the degree of depression was of little consequence to neonatal well-being. It was confirmed that breech presentation and prolongation of the U–D interval are important determinants of depression and birth asphyxia among infants delivered by Caesarean section under general anaesthesia.

General anaesthesia for Caesarean section should maintain unconsciousness in the mother while minimizing any anaesthetic-related depression of the infant. The conflicting requirements of the mother and infant have resulted in the high incidence of maternal "awareness and unpleasant dreams" because, until recently at least, even mild drug-induced depression of the neonate was considered a less acceptable complication of anaesthesia for Caesarean section than maternal awareness. It is now appreciated that minor degrees of drug-induced neonatal depression (especially when caused by a volatile agent, which will be excreted rapidly) are of much less consequence to the well-being of the neonate than depression related to asphyxia. Maternal awareness or unpleasant dreams are likely to provoke considerable emotional reactions in the mother which could lead to fetal asphyxia, a response analagous to that of the fetus to maternal pain in labour, and to induced psychological stress in the pregnant rhesus monkey (Morishima, Pederson and Finster, 1978).

In the maintenance of anaesthesia, the primary issue is the rapidity and efficiency with which the maintenance agent(s) takes over the "role" of the major anaesthetic drug from the induction agent. Fetal well-being requires that oxygen be administered to the mother in a concentration of not less than 50 vol.%—and preferably 65–70 vol.%. Consequently, it is inadvisable to use nitrous oxide as the sole maintenance agent. However, any systemically-administered maintenance agent will achieve undesirable concentrations in the fetus and lead to prolonged depression of the neonate. Thus, the choice has lain between available concentrations of volatile

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agents which, nonetheless, produce two further potential complications. First, myometrial relaxation is induced by most of the volatile agents when given in concentrations at the upper end of the clinical range. Second, deepening the level of sustained anaesthesia will, theoretically at least, tend to prolong the time to recovery.

With these factors in mind, we devised a prospective study of the comparative merits of two volatile agents—trichloroethylene and halothane—administered for the maintenance of anaesthesia in one of several concentrations.

PATIENTS AND METHODS

Anaesthesia

The technique of anaesthesia was standardized. Mothers undergoing elective Caesarean section did not receive a premedicant. All patients had an i.v. infusion of Hartmann's solution in progress and had received the appropriate antacid prophylaxis, using Magnesium Trisilicate mixture BPC. Lateral tilt was provided with a wedge. Pre-oxygenation was carried out for 3–4 min immediately before induction.

The sequence of anaesthesia was: hyoscine 0.4 mg i.v.; cricoid pressure; thiopentone 250–300 mg followed by suxamethonium 100 mg after assurance that anaesthesia had been induced; tracheal intubation and inflation of the cuff; release of cricoid pressure; maintenance of anaesthesia with a mixture of oxygen 8 litre min^{-1}, nitrous oxide 4 litre min^{-1} and a volatile agent. Neuromuscular blockade was provided by an infusion of suxamethonium 1 mg ml^{-1} i.v. Administration of the inhaled mixture and of the suxamethonium continued until the final skin stitch had been tied and the vagina swabbed, with the exception that, in the great majority of patients, the nitrous oxide:oxygen ratio was reversed after delivery.

The choice of volatile agent was made by reference to a series of randomized numbers and lay between the following six options: trichloroethylene 0.2 or 0.3 vol.%, halothane 0.2, 0.3, 0.4 or 0.5 vol.%.

The usual clinical features were observed and, for the purposes of this study, the following were recorded: presentation of fetus at the time of operation; total duration of anaesthesia (min); total amount of suxamethonium given (mg); induction to delivery (I–D) interval (min); uterine incision to delivery (U–D) interval (s); Apgar-minus-colour scores at 1 and 5 min ((A–C)$_1$ and (A–C)$_5$); infant's time to sustained respiration (TSR) (min); requirement to intubate the neonate, as determined by the neonatologist who received the infant; blood loss at operation (estimated by medical and nursing staff), and whether or not blood was transfused during the operation; and time following withdrawal of anaesthesia for mother to regain a "safe" level of consciousness, as assessed by the anaesthetist.

On the day following operation, the mother was asked if she had had any dreams during the operation. If the answer was affirmative, the possibility of "awareness" was pursued.

The operations were classified as either elective or emergency, the former being identified as either group A elective (no evidence suggestive of placental dysfunction) or group B elective.

Means of continuous variables in different sub-groups were compared using appropriate analyses of variance and suitable linear contrasts between means (to compare trichloroethylene and halothane) tested by the relevant *t*-statistic. Frequency data in different groups were compared using chi-squared tests, merging categories where necessary because of small frequencies.

Patients

The series consisted of 777 mothers, of whom 237 underwent elective Caesarean section (183 group A). The distribution in respect to the volatile agent administered is detailed in table I.

RESULTS

Time variables

There was no systematic relationship between the duration of anaesthesia and the type of the volatile agent. The mean values in the 18 sub-groups (three categories of Caesarean section, six categories of maintenance agent) ranged between 37.4 min and 53.9 min.

TABLE I. *Distribution of patients according to category of Caesarean section and identity of volatile agent used to maintain anaesthesia*

	Elective group A	Elective group B	Emergency
Trichloroethylene			
0.2%	38	11	86
0.3%	27	7	94
Halothane			
0.2%	24	12	93
0.3%	38	10	81
0.4%	26	6	95
0.5%	30	8	91

TABLE II. *Mean values (SD) (min) of induction – delivery (I – D) intervals in groups of Caesarean section classified according to type of operation and volatile anaesthetic agent. The symbols T_2, T_3 indicate trichloroethylene 0.2 vol % and 0.3 vol.% and H_2, H_3, H_4, H_5, represent halothane 0.2, 0.3, 0.4 and 0 5 vol.% (in other tables also)*

	T_2	T_3	H_2	H_3	H_4	H_5
Group A	14.7	12.2	13.9	15.0	14.1	14.4
elective	(5.3)	(3.8)	(6.3)	(8.9)	(3.9)	(4.5)
Group B	11.7	9.9	9.9	12.3	8.0	11.9
elective	(5.0)	(3.7)	(4.6)	(4.5)	(2.8)	(2.1)
Emergency	10.0	10.3	10.3	9.5	10.2	10.8
	(3.6)	(4.3)	(4.5)	(4.2)	(4.3)	(4.6)

In regard to the induction–delivery (I–D) interval (table II), consideration of each of the three major categories of Caesarean section revealed no significant differences between the volatile agents and no evident pattern between the mean values. There was no statistically significant difference relating to the type of Caesarean section (ignoring the type of volatile agent) although the mean values in the group A sections were, in each set, higher than those in the other two categories.

Similar analyses of the uterine incision–delivery (U–D) interval (table III) revealed no consistent relationships with agent other than a significantly ($P < 0.025$) shorter mean interval in both groups of elective section conducted under halothane 0.2 vol.%.

Total dose of suxamethonium

A markedly lower mean dose of suxamethonium was administered in each of the three groups of Caesarean section conducted under the higher concentrations of halothane. For example, among group A elective sections the mean dose was 502.0 mg in association with halothane 0.2 vol.% and 363.5 mg in association with halothane 0.5 vol.%. The level of significance showing differences between agents among group A elective and the emergency sections was $P < 0.001$ and among group B sections $P < 0.05$.

TABLE III. *Mean values (SD) (s) of uterine incision to delivery (U – D) intervals in groups of sections classified according to type of operation and the volatile anaesthetic agent*

	T_2	T_3	H_2	H_3	H_4	H_5
Group A	83.5	69.0	50.8	83.5	78.1	84.9
elective	(39.0)	(38.6)	(29.3)	(50.8)	(36.7)	(44.2)
Group B	63.2	57.0	55.5	64.0	58.7	65.4
elective	(39.7)	(31.0)	(25.4)	(46.1)	(17.0)	(26.9)
Emergency	58.3	57.5	72.6	69.3	69.5	71.2
	(37.3)	(33.5)	(54.7)	(49.1)	(44.6)	(54.8)

Maternal weight

There was no evident relationship, either in the entire series or in each set of sub-groups, between maternal weight and either the duration of anaesthesia or the total dose of suxamethonium.

Time to maternal recovery (table IV)

Among group A elective sections a high concentration of halothane was associated with a long time before the mother reached a "safe level of consciousness" ($P < 0.001$). This contrast was not seen between the two concentrations of trichloroethylene studied.

Among emergency sections, the mean time to recovery in the trichloroethylene 0.3 vol.% set was significantly longer than that in the trichloroethylene 0.2 vol.% set ($P < 0.05$), and there was a significant dose effect when comparing the four halothane sets ($P < 0.01$).

The most protracted periods relating to each of the agents ranged from 22 min (halothane 0.3 vol.% and 0.4 vol.%) to 35 min (halothane 0.2 vol.%).

Blood loss (table V)

The errors inherent in the crude estimation of blood loss are well known. We attempted to decrease the influence of these by attending only to instances in which the amount of loss was estimated to exceed 1 litre. We hoped also to strengthen any conclusions which might be drawn, by examining the frequency of intraoperative blood transfusion, although a decision by the anaesthetist to commence blood transfusion was dependent upon several factors, including his estimate of the amount of blood shed.

TABLE IV. *Mean values (SD) (min) of time elapsing between withdrawal of anaesthesia and recovery of mother to a "safe level of consciousness", in groups of Caesarean section classified according to type of operation and the volatile agent*

	T_2	T_3	H_2	H_3	H_4	H_5
Group A	11.5	8.7	5.8	7.2	7.3	9.2
elective	(5.6)	(3.0)	(2.9)	(3.1)	(4.0)	(4.3)
Group B	9.5	12.2	8.7	7.5	7.0	9.5
elective	(5.7)	(5.3)	(8.5)	(4.6)	(5.1)	(5.1)
Emergency	10.1	11.5	7.4	8.4	9.3	10.2
	(3.7)	(4.7)	(3.7)	(4.3)	(4.1)	(4.3)

TABLE V. *Patients grouped according to type of operation and volatile agent administered. Percentage incidence, in each category, of blood loss estimated to exceed 1 litre, and of occasions when blood tranfusion was initiated during operation*

	T_2	T_3	H_2	H_3	H_4	H_5
Elective						
n	49	34	36	48	32	38
>1000 ml	2.0	11.8	5.6	6.2	12.5	7.9
Blood transfused	10.2	14.7	5.6	8.3	11.8	7.9
Emergency						
n	86	94	93	81	95	91
>1000 ml	7.0	3.2	6.5	7.4	12.6	4.4
Blood transfused	17.4	17.0	6.5	11.1	12.6	2.2

Neither estimated blood loss nor initiation of a blood transfusion showed any consistent relationship either with category of section or with the concentration of halothane being administered; the incidence of transfusion matched well the incidence of blood loss exceeding 1 litre. However, in the trichloroethylene series, the incidence of transfusion was greatly in excess of the incidence of estimated blood loss in excess of 1 litre, and was significantly ($P < 0.01$) greater than the incidence of transfusion in the total halothane series. We can offer no explanation for this contrast between the two volatile agents, other than that they could be chance observations.

Awareness and unpleasant dreams (table VI)

The incidence of these complications was too small to permit the realistic application of tests of significance when the series was considered in groups defined by types of Caesarean section. The entire series showed a significantly higher incidence of awareness or unpleasant dreams, or both, when trichloroethylene 0.2 vol.% was compared with 0.3 vol.% ($P < 0.01$), and when halothane 0.2 vol.% was compared with the remainder of the halothane sets ($P < 0.001$).

TABLE VI. *Number of instances of awareness and of unpleasant dreams, and percentage incidence of those complications combined, in the total series grouped according to the characteristics of the volatile anaesthetic agent administered*

	T_2	T_3	H_2	H_3	H_4	H_5
No. patients	135	128	129	129	127	129
Awareness	7	1	9	3	2	0
Unpleasant dreams	6	0	4	3	0	0
Percent combined complications	9.6	0.8	10.1	4.7	1.6	0

TABLE VII. *Distribution of 1- and 5-min Apgar-minus-colour scores among infants in the group A elective series, who presented by the vertex at the time of operation. Groups classified according to agent The mean values of the I – D and U – D intervals in the whole series of group A elective sections, vertex presentations, are also shown*

	T_2	T_3	H_2	H_3	H_4	H_5	Mean I–D (min)	Mean U–D (s)
n	26	21	22	23	21	24	137	137
$(A-C)_1$								
0–3	4	1	0	2	1	1	14.6	85.0
4–6	1	3	2	6	3	3	18.8	76.8
7/8	21	17	20	15	17	20	13.8	68.8
$(A-C)_5$								
<7	1	3	0	1	1	2		
7	2	0	0	3	1	0		
8	23	18	22	19	19	22		

The distribution of 1- and 5-min (A–C) scores among vertex-presenting infants (table VII) did not suggest that these were systematically influenced by the choice of volatile agent.

Considering the entire series without regard to the agent used, a long I–D interval was found to be associated with a low $(A–C)_1$ score ($P < 0.01$), and there was a tendency, not statistically significant, for a long U–D interval to be associated with a low $(A–C)_1$ score. No such trends were observed with regard to the $(A–C)_5$ scores.

Time to sustained respiration (TSR) and requirement to intubate the infant

Amongst group A elective Caesarean sections, a significantly ($P < 0.005$) higher proportion (83.2%) of infants presenting by the vertex had a TSR of less than 1 min compared with those presenting by the breech (62.8%). A significantly ($P < 0.005$) lower proportion (8.8%) of vertex-presenting infants required intubation than of breech-presenting infants (27.9%).

For group A vertex-presenting infants (table VIII), there was no consistent relationship between the volatile agent used and either the duration of TSR or the requirement to intubate. Within the

TABLE VIII. *Number of vertex-presenting infants among group A elective sections, whose TSR was at least 1 min, and number who required intubation. Groups classified according to agent*

	T_2	T_3	H_2	H_3	H_4	H_5
n	26	21	22	23	21	24
$\mathrm{TSR} \geqslant 1$	6	3	1	5	3	5
Intubated	3	1	0	4	1	3

TABLE IX. *Incidence of infants with time-to-sustained respiration (TSR) of at least 1 min, and of infants requiring tracheal intubation in the course of resuscitation, within the entire series, categorized in respect to the volatile agent administered to the mother*

	T_2 135	T_3 128	H_2 135	H_3 129	H_4 127	H_5 129
Per cent TSR > 1 min	33.1	33.6	29.4	37.8	38.6	41.7
Per cent requiring intubation	17.8	22.8	19.7	23.4	27.0	26.6

entire series, comparing groups with TSR less than 1 min with those with TSR 1–3 *v.* TSR 4–9, there were no significant differences between the mean values of either the I–D interval or the U–D interval, and there was no association between the duration of either interval and the requirement for intubation.

Analysis of the data from the complete series revealed an apparent tendency, which did not reach the level of statistical significance, for a greater incidence of TSR > 1 min and of the requirement to intubate, with increasing concentrations of the volatile agent (table IX).

DISCUSSION

This study has revealed no consistent association which could have clinical importance, between the volatile anaesthetic agent administered, or the category of Caesarean section, and: the total duration of anaesthesia; the induction-delivery interval; or the uterine incision-to-delivery interval.

Use of the higher concentrations of halothane was associated with a lower total dose of suxamethonium. There is no evidence to suggest that the association was influenced by either the duration of anaesthesia or maternal weight.

The time taken after cessation of anaesthesia for the mother to recover a level of consciousness such that she could safely be left in the care of the midwifery staff was affected by the volatile agent, time to recovery increasing with increasing concentration. However, the difference between the shortest mean time and the longest was only 4.4 min, which cannot of itself be said to provide a reasonable argument for choosing one agent rather than the other.

The most striking observation relating to the choice of volatile agent concerns the complication of "awareness plus unpleasant dreams". The possibility of this complication has been known for many years, and one objective of this study was to find a way of reducing its incidence without exposing either mother or infant to harm. Our results clearly show that trichloroethylene 0.2 vol.%, halothane 0.2 vol.% or halothane 0.3 vol.% (together with a 30:70 mixture of nitrous oxide in oxygen) produces an unacceptably high incidence of "awareness plus unpleasant dreams". A better choice must be trichloroethylene 0.3 vol.%, or halothane 0.4 vol.% or 0.5 vol.%, none of which appears to be associated with a higher incidence of other maternal complications.

However, the period of recollection during operation was invariably confined to that around the time of delivery. This suggests that there are differences in the speed at which each concentration of volatile agent can "take over" the role of primary anaesthetic agent from thiopentone rather than their respective abilities to provide anaesthesia. The relatively small differences in recovery time add substance to this.

It was reassuring to note that the incidence of neonatal depression—as defined by the 1- and 5-min Apgar-minus-colour scores, the time to sustained respiration and the incidence of active resuscitation (endotracheal intubation)—was lowest in the series of group A elective sections and highest in the group of emergency sections. For group A elective section, the type of agent did not notably effect the incidence of any of the attributes of neonatal depression, whether the infant presented by the vertex or the breech.

Analysis of the entire data suggested a possible tendency for longer TSR and an increased incidence of required intubation to be associated with higher concentrations of the volatile agents. This would suggest that, if the fetus is compromised before or during Caesarean section, the use of the higher concentration may cause more respiratory depression of the neonate than the lower concentration. There was also, in the entire series, a tendency for prolongation of the I–D interval and of the U–D interval to be associated with a low $(A–C)_1$ score, but not with the other stigmata of neonatal depression. The results indicate that the choice of trichloroethylene 0.3 vol.%, or halothane 0.4 or 0.5 vol.% virtually eliminates the complication of "awareness plus unpleasant dreams" without posing additional hazard to the mother or neonate. The latter finding confirms in respect of awareness and blood loss, those reported by Moir (1970). The possible slight increase in the incidence of neonatal respiratory depression resulting from use of these concentrations in circumstances in which the fetus is already compromised is likely to be of very little consequence to the ultimate well-being of the infant. The results also confirm that, when Caesarean section is performed under general anaesthesia, infants presenting by the breech are at greater hazard than are appropriately matched vertex-presenting infants.

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FADE CHARACTERISTICS AND ONSET TIMES FOLLOWING ADMINISTRATION OF PANCURONIUM, TUBOCURARINE AND A MIXTURE OF BOTH AGENTS

J. N. CASHMAN, R. M. JONES AND L. M. VELLA

SUMMARY

The onset characteristics of pancuronium, tubocurarine and a mixture of these two neuromuscular blocking drugs were studied during the induction of neuromuscular blockade, using a train-of-four pattern of stimulation. Four characteristics of onset were defined: train-of-four fade = a reduction in the height of the fourth twitch greater than a reduction in the height of the first twitch; latent onset time = time from injection of neuromuscular blocker to a greater than 5% reduction in the first twitch in the train-of-four; total onset time = time to 90% reduction in twitch height; manifest onset time = time from 5% to 90% reduction in twitch height. Tubocurarine was associated with significantly more fade than either pancuronium or the mixture. During the period of study the fade profile of the mixture was almost identical to that of pancuronium alone. The mixture had the most rapid total onset time (100.3 s), tubocurarine the slowest (135.1 s) and pancuronium was intermediate (124.0 s). The mixture and tubocurarine had similar latent onset times, while the mixture and pancuronium had similar manifest onset times.

Potentiation of neuromuscular blockade when mixtures of certain non-depolarizing agents are administered has been demonstrated *in vitro* (Pollard and Jones, 1983) and *in vivo* (Wong, 1969). Although the overall speed of onset of neuromuscular blockade has been extensively investigated, few studies have specifically measured other facets of the onset characteristics of myoneural blockers. This study was designed to investigate the onset characteristics of pancuronium, tubocurarine and a mixture of both of these agents, in terms of:

(1) Depression of the first twitch in the train-of-four.
(2) The degree of train-of-four fade.
(3) The latent, manifest and total onset times.

PATIENTS AND METHODS

The study was approved by the hospital Ethics committee and 24 ASA class I patients of either sex scheduled to undergo routine surgical procedures gave their informed consent to inclusion. Their ages ranged from 19 yr to 46 yr, and their weights from 42 kg to 80 kg; no patient of greater than 10% above ideal weight was included in the study. Patients were allocated at random to one of three groups to receive tubocurarine 0.6 mg kg^{-1}, pancuronium 0.1 mg kg^{-1}, or a mixture of these two relaxants (pancuronium 0.05 mg kg^{-1} plus tubocurarine 0.3 mg kg^{-1}).

Anaesthesia was induced with thiopentone 200–400 mg and maintained with nitrous oxide in oxygen delivered via a Bain type coaxial breathing system and face mask, with additional 50-mg increments of thiopentone administered as needed. The non-dominant arm was immobilized in a splint and the ulnar nerve stimulated at the wrist via surface electrodes connected to a Myotest nerve stimulator delivering train-of-four supramaximal square wave pulses at 2 Hz of 0.2 ms duration repeated every 10 s. The evoked force of contraction of the adductor pollicis muscle was measured by a Grass force displacement transducer connected to a Devices preamplifier and chart recorder.

After control readings had been obtained, the neuromuscular blocking drug was injected i.v. to

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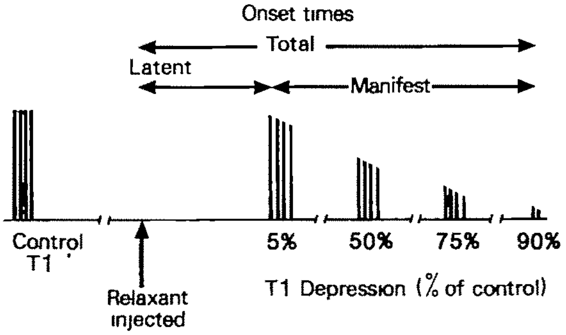

FIG 1. Summary of indices measured.

the contralateral arm and flushed by a fast running infusion. T1 depression (reduction in the height of the first twitch (T1) in the train-of-four relative to control T1) and the reduction in the T4 ratio (height of the fourth twitch (T4) relative to the height of T1) were recorded. Three features of onset time were derived from the recordings: *total onset time* was defined as the time from injection of the myoneural blocking drug to a 90% reduction in T1; *latent onset time* was defined as the time from injection of the myoneural blocker to the first clearly (> 5%) reduced T1; and *manifest onset time* was defined as the time from the first clearly reduced T1 to 90% T1 depression (Minsaas and Stovner, 1980). We also measured fractional manifest onset times to 50% and 75% T1 depression (fig. 1). All measurements were completed before the commencement of surgery.

All results are expressed as mean (SD) and statistical analysis was performed using unpaired Student's *t* test.

RESULTS

The three groups were comparable in respect of age, weight and pre-induction haemodynamic values (table I). One patient was excluded from statistical analysis as a result of a violation of the experimental programme, thus seven patients received tubocurarine, seven received pancuronium and nine received the mixture.

TABLE II. *Mean (SD) T4 ratios at 25%, 50% and 75% T1 depression.* **Significantly more fade than pancuronium* (P<*0.05*) *or the mixture* (P<*0.01*)

	T1 depression		
	25%	50%	75%
Tubocurarine	0.81 (0.07)	0.70 (0.10)	0.41 (0.18)*
Pancuronium	0.80 (0.05)	0.72 (0.04)	0.61 (0.18)*
Mixture	0.81 (0.03)	0.75 (0.05)	0.61 (0.09)

During the onset of neuromuscular blockade, at 75% T1 depression tubocurarine was associated with significantly more T4 fade than was either pancuronium ($P < 0.05$) or the mixture of pancuronium and tubocurarine ($P < 0.01$) (table II); the degree of T4 fade at 75% T1 depression was identical for pancuronium and the mixture of pancuronium and tubocurarine (0.61). In addition, T1 depression at the point when the fourth twitch disappeared was significantly greater following tubocurarine than following pancuronium ($P < 0.01$), or the mixture ($P < 0.01$) (table III). Again, these values were identical for pancuronium and the mixture of pancuronium and tubocurarine (6%). Furthermore, the equations for the regression lines of T1 depression *v.* T4 ratio for pancuronium and the mixture were very similar, but differed from that for tubocurarine (fig. 2).

TABLE III. *Mean (SD) T1 depression (%) at disappearance of T4.* **Significantly greater* (P<*0.01*) *than with pancuronium or with the mixture*

Tubocurarine	13 (4)*
Pancuronium	6 (3)
Mixture	6 (2)

TABLE I. *Mean (SD) age, weight and pre-induction haemodynamic variables. HR = heart rate; MAP = mean arterial pressure*

	Age (yr)	Weight (kg)	HR (beat min^{-1})	MAP (mm Hg)
Tubocurarine (*n*=7)	32.4 (6.6)	62.7 (10.6)	74.3 (8.8)	85.1 (8.6)
Pancuronium (*n*=7)	35.3 (9.6)	65.0 (9.7)	77.4 (8.7)	90.3 (3.0)
Mixture (*n*=9)	33.0 (9.5)	59.0 (12.0)	74.2 (11.7)	84.4 (10.1)

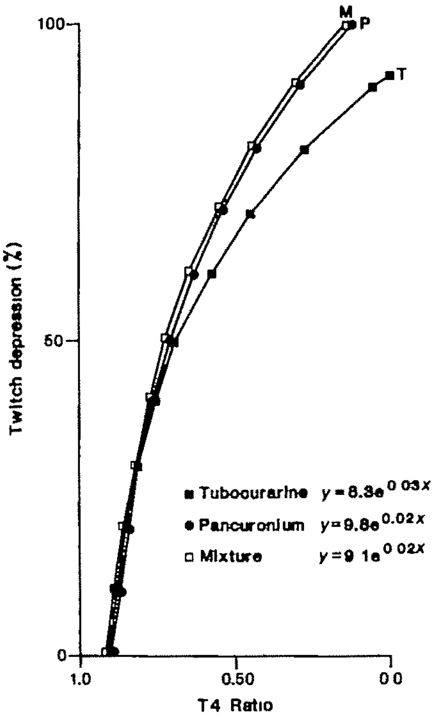

FIG. 2. T4 fade during onset of blockade.

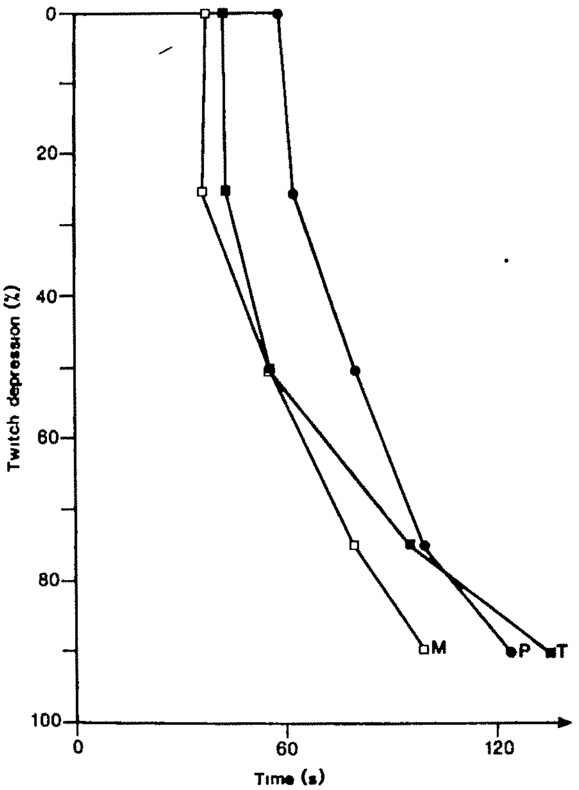

FIG. 3. Speed of onset of pancuronium (P), tubocurarine (T), and the mixture (M), as indicated by percent depression of twitch height from control. The horizontal line at 0% indicates latent onset times.

It can be seen (table IV, fig. 3) that pancuronium had a longer and more variable latent onset time than either tubocurarine or the mixture, but tubocurarine, although having an initially more rapid manifest onset time (to 50% T1 depression), had a longer overall manifest onset time (to 75% and 90% T1 depression); the onset time curves of pancuronium and of tubocurarine cross at about 80% twitch depression. The mixture had the shortest latent onset time, but thereafter behaved in a manner almost identical to that of pancuronium. It thus had a faster overall total onset time and achieved 90% twitch depression more rapidly than either drug on its own, although these differences were not statistically significant.

TABLE IV. *Latent, manifest and total onset times for the three drug regimens*

	Neuromuscular blocking drug		
Onset times (s)	Tubocurarine	Pancuronium	Mixture
Latent	41.3 (19.1)	56.0 (33.6)	36.3 (8.5)
Manifest to:			
50%	14.0 (10.5)	23.0 (18.8)	18.6 (12.2)
75%	53.5 (37.7)	43.0 (19.0)	43.0 (18.2)
90%	94.0 (56.3)	68.4 (32.5)	64.4 (21.9)
Total to:			
50%	55.2 (28.2)	78.6 (44.8)	54.9 (19.2)
75%	94.8 (55.9)	98.7 (44.3)	79.2 (25.4)
90%	135.1 (73.5)	124.0 (55.0)	100.3 (29.2)

DISCUSSION

It is likely that single twitch depression and train-of-four fade represent the interaction of neuromuscular blocking drugs at different sites within the neuromuscular junction (Bowman, 1980). Although there is still some disagreement, a site other than the post-synaptic cholinoceptor, possibly situated presynaptically, would seem likely to be responsible for fade.

We have demonstrated that both pancuronium and the mixture of pancuronium and tubocurarine, in the doses outlined, are associated with very similar degrees of T4 fade when onset of neuromuscular blockade reaches 75% T1 depression, and that tubocurarine alone is associated with significantly more fade. Williams, Webb and Calvey (1980) also observed that tubocurarine was associated with significantly more fade during onset than was pancuronium. However, it is noteworthy that the fade characteristics of our mixture were identical (at 75% T1 depression) with those of pancuronium alone; this was an unexpected observation. On the assumption that a pre-synaptic receptor is responsible for fade, tubocurarine would appear to have less affinity for these receptors in the presence of pancuronium.

The presence of pancuronium in a mixture with tubocurarine modified the effect of tubocurarine on T1 depression also. It would appear that the presence of one drug may alter the affinity of the other for the receptor responsible for T1 depression, for the receptor responsible for T4 fade, or for both. Interactions between neuromuscular blocking drugs are also reflected in a comparison of onset times of the individual drugs with those of the mixture.

We excluded several factors which influence the speed of onset achieved with neuromuscular blocking agents: the dose administered, the effect of inhalation anaesthetic agents (Auer and Meltzer, 1914; Pollard and Miller, 1973), increasing age (Feldman, 1976), obesity (Vaughan, 1974) and variation in haemodynamic parameters (Feldman, 1976; Goat et al., 1976). We did not admit to the study any patient older than 50 yr, and thus have investigated a younger group of patients, with apparently normal circulation times as suggested by their pre-induction haemodynamic values. No patient of greater than 10% above ideal weight was included in the study. The potential effect of inhalation agents was eliminated by avoiding their use during the period when neuromuscular blockade was being studied. Thus, the onset times—latent, manifest and total—can be expected to reflect the characteristics of the individual agents used. In these circumstances the present study appears to demonstrate that:

(1) Tubocurarine has a shorter latent onset time than pancuronium.

(2) Pancuronium has a more variable latent onset time.

(3) Pancuronium has an overall more rapid manifest onset time.

Consequently, the onset curves of tubocurarine and pancuronium cross at a T1 depression of approximately 80% (fig. 3).

The marked variability in latent onset observed with pancuronium (Blackburn and Morgan, 1978; Minsaas and Stovner, 1980; Williams, Webb and Calvey, 1980) and the crossing over of the onset curves of pancuronium and tubocurarine (Blackburn and Morgan, 1978), are findings which have been noted by other workers also. The precise significance of the latter observation remains unclear, although it may be the result of a differential rate of penetration into the synaptic cleft by the individual agents (Waud, 1967; Blackburn and Morgan, 1978; Hull, 1982). Although the differences in onset time in our study did not achieve statistical significance, our result for the total onset time of pancuronium 0.1 mg kg^{-1} is within 10% of the values obtained by other investigators (Blackburn and Morgan, 1978; Minsaas and Stovner, 1980). The mixture of pancuronium with tubocurarine appears to have the more rapid latent onset time of tubocurarine, and the more rapid manifest onset time of pancuronium and, thus, a total onset time which is more rapid than either drug alone. This might be anticipated, given the association between dose of neuromuscular blocking drug and speed of onset, and the fact that mixtures of pancuronium and tubocurarine have been shown to be synergistic (Duncalf et al., 1983; Pollard and Jones, 1983).

In conclusion, we have shown that mixtures of neuromuscular blocking drugs do not necessarily have onset characteristics which are simply a composite of the individual agents. This suggests that, within the neuromuscular junction, the site(s) or mechanism(s) of action of an individual neuromuscular blocker may be altered by the presence of another blocking agent. This may, in part at least, explain the observed differences in the latent, manifest and total onset times of the mixture of pancuronium and tubocurarine compared with those of the individual agents. That the total onset time of neuromuscular blockade may be reduced by administering mixtures of neuromuscular blocking drugs may have clinical significance.

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CIRCULATORY RESPONSES TO THIOPENTONE AND TRACHEAL INTUBATION IN PATIENTS WITH CORONARY ARTERY DISEASE

Effects of Pretreatment with Labetalol

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Laryngoscopy and tracheal intubation are often accompanied by increases in heart rate and arterial pressure (Wycoff, 1960; Prys-Roberts et al., 1971) which may lead, in patients with coronary artery disease, to myocardial ischaemia. Several methods have been proposed to suppress the circulatory responses to intubation: topical anaesthesia or the use of parenteral lignocaine, induction of anaesthesia using high dose of fentanyl, the supplementation of thiopentone with smaller doses of fentanyl, the use of vasodilators or beta-adrenoceptor blocking agents.

Although it is customary to maintain patients with coronary artery disease on their preoperative beta-adrenergic blocking regimen, conflicting results have been published on the haemodynamic responses to intubation in such patients (Prys-Roberts et al., 1973; Siedlecki, 1975; Rhyanen et al., 1977; Kopriva, Brown and Pappas, 1978; Fassoulaki, Kaniaris and Kotsanis, 1980; Werner et al., 1980; McCammon, Hilgenberg and Stoelting, 1981; Safwat et al., 1981; Magnusson et al., 1983).

This study, on patients with coronary artery disease, investigated the efficacy of an infusion of labetalol in decreasing the circulatory responses to intubation. Labetalol (Wallin and O'Neill, 1983) is the prototype of a new class of antihypertensive agents that blocks competitively both beta- and alpha-adrenergic receptors. Although a central action has been demonstrated (Devoto et al., 1980), labetalol does not readily cross the blood–brain barrier (Martin, Hopkins and Bland, 1976).

SUMMARY

The haemodynamic responses to induction and tracheal intubation have been studied in patients with coronary artery disease randomly assigned to a labetalol pretreatment group ($n = 14$) or to a placebo group ($n = 16$). Twelve hour before operation, treated patients received a bolus dose of labetalol 0.5 mg kg^{-1} followed by a constant infusion of 0.1 mg kg^{-1} h^{-1} i.v. Anaesthesia was induced with thiopentone and phenoperidine, and intubation performed following the administration of suxamethonium. At intubation, the changes in heart rate ($P < 0.01$), mean arterial pressure ($P < 0.05$) and rate–pressure product ($P < 0.01$) were significantly smaller in the labetalol group compared with the placebo group. Labetalol pretreatment appears satisfactory and may be useful in patients with coronary artery disease who have a normal left ventricular ejection fraction.

PATIENTS AND METHODS

Thirty patients scheduled for major surgery were studied and allocated randomly to placebo ($n = 16$) or labetalol ($n = 14$) groups in a double-blind study. All patients had a history of stable angina (N.Y.H.A. classes 2 and 3). Patients with a left ventricular ejection fraction < 0.55 were excluded, as were patients already receiving beta blocking drugs. Long-acting nitrates or calcium antagonists, or both, were administered up to the evening before surgery, then the patients remained at rest. The study was approved by the hospital Ethics Committee and informed consent was obtained from each patient.

Twelve hour before surgery a triple-lumen pulmonary artery catheter and a radial artery catheter were inserted under local anaesthesia, after which an

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infusion of placebo or of labetalol 0.5 mg kg^{-1} as a bolus dose followed by a constant infusion of 0.1 mg kg^{-1} h^{-1} was started via a peripheral vein. ECG lead V5 was monitored throughout the study.

Premedication consisted of flunitrazepam 1 mg i.m. and atropine 0.5 mg i.m., 1 h before the induction of anaesthesia with phenoperidine 2 mg and thiopentone 5–7 mg kg^{-1}. Suxamethonium 1 mg kg^{-1} was administered and nasortachea intubation undertaken following ventilation with oxygen via a face mask. Anaesthesia was maintained with nitrous oxide in oxygen (FI_{O_2} = 0.4) plus additional phenoperidine as required.

The following haemodynamic indices were recorded: heart rate, arterial pressure, pulmonary capillary wedge pressure, and cardiac output using the thermodilution technique. Cardiac index, systemic vascular resistance index and rate–pressure product were calculated using standard formulae (cardiac index = cardiac output/body surface area; systemic vascular resistance index = mean arterial pressure – mean right atrial pressure/cardiac index; rate–pressure product = systolic arterial pressure × heart rate).

All these haemodynamic measurements were performed before the infusion of labetalol, 1 h after the beginning of the infusion, before the induction of anaesthesia, immediately following tracheal intubation, and 5 min later; heart rate and arterial pressure were recorded every hour following the bolus dose of labetalol.

Clinical differences between groups were evaluated using the chi-square analysis. The Mann–Whitney (two-sided) rank sum test for unpaired data was used for between-group comparisons. The significance of changes within groups was analysed with the Wilcoxon (two-sided) rank sum test for paired data. Probability values less than 0.05 were considered to indicate statistical significance.

RESULTS

Results are expressed as mean ± SD.

The characteristics of the patients are shown in table I. Age, weight, sex, number of previous infarctions, number of hypertensive patients and left ventricular ejection fraction were identical in both groups (table I). The haemodynamic data are summarized in figure 1.

Both groups were identical as far as baseline values were concerned, and there were no changes in the haemodynamic variables during the 12 h of preoperative surveillance in both groups.

At the time of intubation, the heart rate, arterial pressure and systemic vascular resistance index, were significantly different ($P < 0.01$) from the pre-induction value in the placebo group. In the labetalol group, systemic vascular resistance index was increased compared with preinduction values ($P < 0.05$).

At the time of intubation, rate–pressure product increased significantly in both groups ($P < 0.01$ in the placebo group; $P < 0.05$ in the labetalol group). In 13 patients in the placebo group (mean value: 14.900 ± 4300) and in three patients in the treated group (mean value: 10.100 ± 3200) the rate–pressure product was greater than 11 000 during intubation ($P < 0.01$).

At the time of intubation, differences *between* the groups could be documented only for heart rate ($P < 0.01$), mean arterial pressure ($P < 0.05$) and rate–pressure product ($P < 0.05$).

In both groups haemodynamic values after intubation were similar to those measured before induction of anaesthesia.

ST segment depression was observed immediately after intubation in three patients in the placebo group, but disappeared after the administration i.v. of nitroglycerine and phenoperidine. Although no changes were noted in the ECG in the labetalol group, the difference between the groups was not significant.

DISCUSSION

Labetalol appears to have the same anti-hypertensive properties as other beta-adrenergic blocking agents (Wallin and O'Neill, 1983); in acute studies

TABLE I. *Preoperative values in control and treated patients (mean ± SD). EF = left ventricular ejection fraction*

	Age (yr)	Sex (M/F)	Weight (kg)	Hypertensive patients (%)	Previous infarction (%)	EF (%)
Placebo (*n*=16)	52 ±7.6	15/1	71.7 ±6.4	25	44	63 ±8.4
Treated (*n*=14)	52.5 ±9.1	12/2	72.4 ±9.4	14	43	64.5 ±9.5

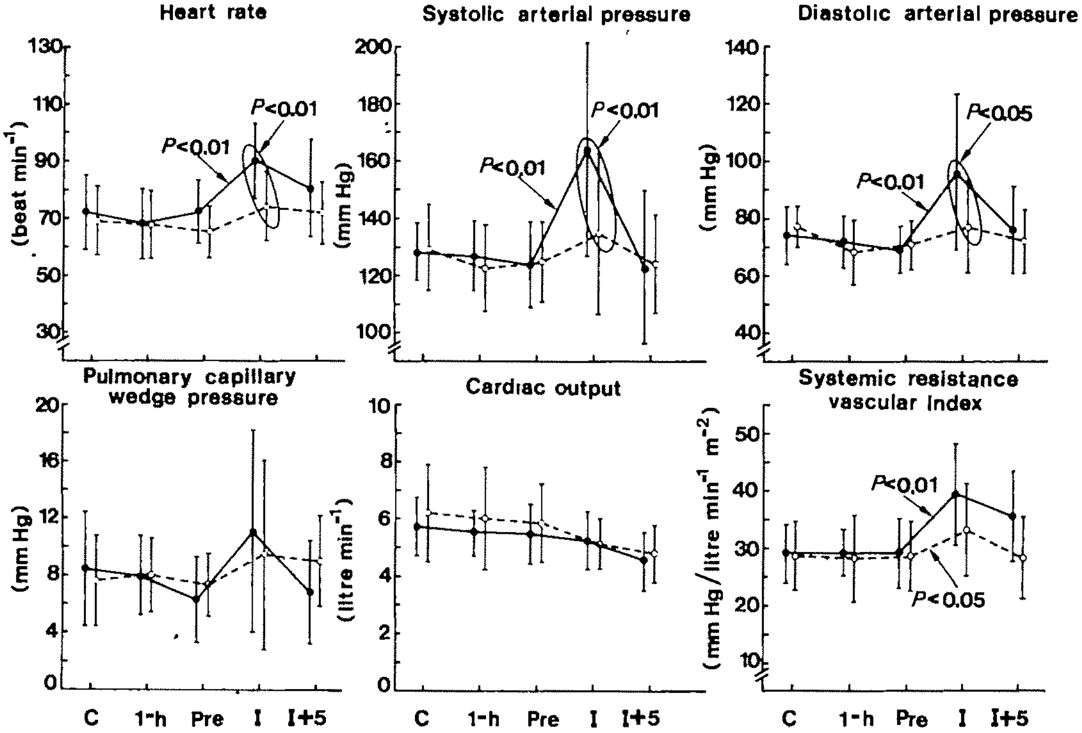

FIG 1. Haemodynamic variables recorded before pretreatment, 1 h after its beginning, before induction, just after intubation and 5 min later (mean ± SD). ●——● = Placebo group (n = 16); ○——○ = Labetalol-pretreated group (n = 14).

(Bahlmann et al., 1979; Koch, 1976) it does not seem to induce any increase in systemic vascular resistance as has been demonstrated following the administration of several beta-adrenergic blocking agents (Taylor, Silke and Lee, 1982). Labetalol has been shown to be effective in the management of hypertension following coronary artery surgery (Morel, Forster and Suter, 1982).

In patients with coronary artery disease, we believe that pretreatment must begin long before the induction of anaesthesia so as to detect possible complications such as hypotension or low cardiac output. Thus, an initial loading dose of labetalol, which was smaller than that usually recommended for hypertensive patients (Pearson and Harvard, 1976), was followed by a constant infusion.

In the placebo group, the results were consistent with those obtained previously by a number of authors: intubation was frequently associated with tachycardia and hypertension (as a consequence of an increase in systemic vascular resistance).

In the test group, the infusion of labetalol did not modify the haemodynamic variables—probably as a result of the small number of hypertensive patients in this group, and of the absence of patients with poor left ventricular ejection fraction. However, a large percentage of the patients, in both groups, had had a previous myocardial infarction. In the pretreated group there was an increase in systemic vascular resistance at the time of intubation but without significant increase in arterial pressure; heart rate also remained unchanged. Rate–pressure product did increase significantly, but it exceeded 11 000 in only 21% of the labetalol-pretreated patients.

The results obtained in the labetalol group are consistent with those of Prys-Roberts and co-workers (1971) and Rhyanen and colleagues, (1977) who noted the efficacy of pretreatment with practolol, and with those of Safwat and associates (1981). However, many other investigators have reported negative results with practolol (Siedlecki, 1975; Werner et al., 1980), propanolol (Kopriva, Brown and Pappas, 1978; McCammon et al., 1981) and metoprolol (Magnusson et al., 1983). These conflicting results can be accounted for by the different anaesthetic techniques used (especially halothane-nitrous oxide anaesthesia) and the different methods of administration of the beta-adrenergic blocking agents.

The part played by the alpha-adrenergic blocking properties of labetalol is not easy to demonstrate in this study; systemic vascular resistance index appeared to increase to a lesser extent in the labetalol group than in the placebo group, but the difference was not significant. Kopriva, Brown and Pappas (1978) studied haemodynamics during intubation in patients receiving propranolol and found a similar increase in systemic vascular resistance in treated and untreated patients.

The method of administration used in this study enabled us to define a standard rate of infusion of labetalol which appeared to suppress the haemodynamic response to intubation and may be useful in patients with coronary artery disease but with normal ventricular function, when a rapid induction of anaesthesia is contemplated.

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EFFECTS OF ENFLURANE ON MYOCARDIAL ISCHAEMIA IN THE DOG

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SUMMARY

The effects of experimentally induced, severe coronary artery stenosis on regional changes in myocardial blood supply, cardiac function, and metabolism were studied in 14 dogs. The anterior interventricular branch of the left coronary artery (LAD) was constricted such that arterial inflow was reduced by 80%. Nine dogs were given enflurane in a concentration of 2.2 vol.% (1 MAC) in air, and five animals received no enflurane (controls). Regional myocardial blood supply was measured by the tracer microspheres technique, using 8-μm microspheres labelled with five different radioisotopes. Regional cardiac function (end-diastolic length of the muscle fibres = EDL; segmental shortening during systole = ΔL) was estimated with the aid of two ultrasonic crystals which were placed in the subendocardial layer of the myocardium supplied by the LAD. Regional myocardial metabolism (oxygen consumption; lactate extraction) was evaluated from arterial and coronary venous blood samples. The latter were collected selectively from the region supplied by the LAD via the great cardiac vein. The results showed that, during severe coronary artery stenosis comparable to clinical conditions, apart from the known actions on systemic haemodynamics and contractility, enflurane had beneficial effects on regional myocardial variables. This was indicated by reduced regional contraction, measured as EDL and ΔL; unchanged subendocardial blood flow without any redistribution; and improved lactate extraction in the ischaemic region.

In patients with coronary artery disease, cardiac function is governed by the oxygen consumption of the myocardium and the oxygen available to the myocardium. The major determinants of cardiac oxygen demand are: heart rate, wall tension, and contractility: an increase in any or all of these increases the requirement for oxygen. Inevitably, this means that the risks of anaesthesia and surgery are increased in patients with coronary artery disease (Tarhan et al., 1972; Topkins and Artusio, 1964). However, under clinical conditions it is difficult to evaluate precisely the effects of anaesthetic agents on myocardial ischaemia—for two main reasons: the extent of ischaemia varies greatly between individual patients, and it is impossible to delineate clearly regional changes in myocardial performance.

We have developed a model of myocardial ischaemia comparable to that obtained clinically, and have investigated the effects of enflurane on regional myocardial blood supply, regional myocardial function and regional myocardial metabolism during severe coronary stenosis.

MATERIALS AND METHODS

Investigations were undertaken on 14 mongrel dogs of either sex with a mean weight of 17.8 ± 5.1 kg. Nine dogs received enflurane in a concentration of 2.2 vol.% (1 MAC; enflurane group; EG) in air. Five animals received no enflurane and served as controls (control group; CG).

Anaesthesia

The dogs were premedicated with morphine 0.4 mg/kg body-weight) and propiolyl-promazine

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(Combelen) 0.2 mg kg^{-1} i.m. Anaesthesia was induced with pentobarbitone sodium 15 mg kg^{-1} i.v., and after tracheal intubation, the lungs were ventilated with 67% nitrous oxide in oxygen using a Dräger Narkosespiromat at a rate of 12 b.p.m. Nitrous oxide was administered during the surgical preparation only. The dogs were then ventilated with an oxygen–air mixture ($F_{I_{O_2}} = 0.33$) during the measurements. The arterial oxygen tension did not exceed 16 kPa and the mean carbon dioxide tension was 5.1 ± 0.27 kPa. Ventilation was monitored by blood-gas analysis (Eschweiler D33) at regular intervals. Any metabolic acidosis was corrected by administration of 8.4% sodium bicarbonate. Anaesthesia was maintained by hourly doses of pentobarbitone 3 mg kg^{-1}.

Core temperature was maintained at 37 ± 1 °C by means of a heating pad. Fluid requirements during operation were supplied by lactated Ringer's solution i.v. Alcuronium was given before the thoracotomy.

Surgical preparation

A large polyethylene (PE) catheter was placed in the femoral vein to allow infusions and injections i.v. Another PE catheter, for continuous pressure measurements (Statham P23Db) was passed into the aortic arch via a femoral artery. Cardiac output was measured by the thermodilution method, the appropriate injection catheter being placed in the right atrium via the external jugular vein. The thermistor was passed into the aortic arch via a small branch of the femoral artery.

A thoracotomy was performed (fifth left intercostal space), the pericardium opened and the anterior interventricular branch of the left coronary artery (LAD) exposed immediately distal to its origin. Care was taken not to damage the closely adjacent coronary vein or the major descending arterial branches. An electromagnetic flowmeter (Statham SP2202) was fixed at this site, and a mechanical coronary constrictor with a micrometer screw gauge (Vetter and Mittmann, 1981) sited distal to the flowmeter. A flexible PE catheter was inserted, via the coronary sinus, to the great cardiac vein for selective collection of coronary venous blood from the LAD region (Obeid et al., 1972). A surgical snare was used to compress the vein during blood sampling, and pr vent any backflow from the coronary sinus (fig. 1

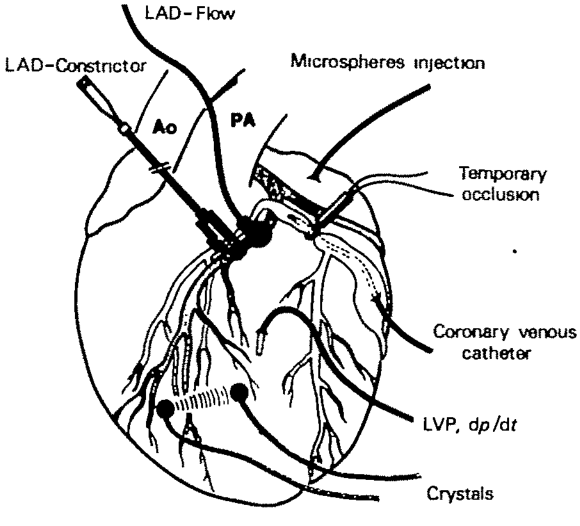

FIG. 1. Diagram of the experimental procedure. LAD = left anterior descending coronary artery; Ao = aorta; PA = pulmonary artery; LVP = left-ventricular pressure; d*p*/d*t* = first derivative of LVP.

A microtip manometer (Millar PC350) was plac transmurally into the left ventricle to measure tl left ventricular pressure (LVP) and its first deriv tive (d*p*/d*t*). A silicone catheter was tied into the le auricle for the injection of radioactive microspheres. The shortening of the regional muscle fibres was estimated with the aid of two ultrasonic crystals which were placed in the subendocardial layer of the area of myocardium supplied by the LAD (fig. 1).

Haemodynamics

The following variables were recorded continuously on an eight-channel recorder (Brush Mk481): Lead II electrocardiogram (ECG) using needle electrodes, LVP, d*p*/d*t*, left ventricular end-diastolic pressure (LVEDP), aortic pressure, coronary flow in the LAD (CF_{LAD}), and shortening of the regional muscle fibres in the area supplied by the LAD (ΔL).

Coronary perfusion pressure (CPP) was calculated as diastolic pressure minus the LVEDP. Cardiac contractility was estimated as the so-called Krayenbuehl contractility index (KI) and was calculated using the following formula (Krayenbuehl, 1967, 1969):

$$KI = \frac{dp/dt_{max}}{IP} \ (s^{-1})$$

where IP = instantaneously developed pressure.

Regional myocardial function

One pair of ultrasonic transducers (Parks Electronics, Beaverton, U.S.A.) was placed in the subendocardial layer at right angles to the axis of the heart (Franklin et al., 1973; Hagl et al., 1977). The site was selected so that both crystals were placed in the area of the myocardium supplied by the LAD. By measuring continuously the ultrasound transit times between both crystals, it was possible to trace regional wall movement of the left ventricle quantitatively and qualitatively. The end-diastolic length (EDL) and the length at the end of the ventricular systole (ESL) were measured. As the distances between the crystals differed in the various experiments, these were standardized to a baseline segmental length of 10 mm by means of the following formula (Theroux et al., 1976):

$$\mathrm{EDL_{corr}} = \frac{\mathrm{EDL} \cdot 10}{\mathrm{EDL_{baseline\ value}}}\ \text{(mm)}$$

The extent of the segmental shortening during systole (ΔL) was calculated as the difference between EDL and ESL divided by EDL. ΔL was expressed in percent of the EDL. The standardization was carried out in accordance with the above formula.

Regional myocardial blood flow

Myocardial blood flow (MBF) was determined with the aid of tracer microspheres (Rudolph and Heymann, 1967). Microspheres (3M Company) with a mean diameter of 8 µm and labelled with five different radioisotopes (iodine-125, cerium-58, chromium-51, strontium-85, scandium-46) were injected to the left atrium at the measuring times. During the injection of the microspheres, a reference blood sample was drawn through a catheter in the carotid artery the tip of which rested in the arch of the aorta (Domenech et al., 1969).

When all measurements were completed, the LAD was ligated and the pressure was measured distal to the occlusion ("retro-pressure"). The ratio of the retro-pressure and mean aortic pressure (MAP) served as a measure of the collateral blood supply of the area supplied by the LAD. This ratio was invariably less than 0.3, that is there was no extensive collateral supply.

At the end of the experiment, the occluded LAD was injected with 20 ml of a saturated potassium chloride solution mixed with lissamine green. The green-stained part of the myocardial tissue represented the area supplied by the LAD. The heart was divided into several samples (Wirth et al., 1979). Each sample was subdivided into three layers, subendocardium, myocardial third, and subepicardium and the MBF in each sample was determined by measurement of the radioactivity in relation to the reference blood sample.

Myocardial metabolism

In order to assess the metabolic processes in the ischaemic area of the myocardium, coronary venous blood was selectively sampled via the great cardiac vein from the region supplied by the LAD. The following variables were estimated in samples of arterial and coronary venous blood: the concentrations of potassium, sodium, lactate, pyruvate, CK-MB (Boehringer) and haemoglobin, the haematocrit, pH, $P\mathrm{CO_2}$, $P\mathrm{O_2}$, and oxygen content (Lexington Instruments, Waltham, U.S.A.).

Experimental procedure

The individual sections of the experimental procedure are shown in table I. MBF was determined (tracer microspheres) at points 2, 4, 6, 8 and 10. The control group (CG) received no enflurane at stages 5 and 6.

Statistics

The results are presented as means ± standard error of the mean (SEM). Differences between the mean values were evaluated for statistical significance by Student's paired and unpaired *t* tests, and were considered significant at P values $\leqslant 0.05$.

RESULTS

Haemodynamic variables (table II)

The coronary stenosis had no effect on the mean aortic pressure (MAP) or the left ventricular pressure (LVP). The only reaction to the acute ischaemia

TABLE I. *Outline of the experimental design*

Episode	Time (min)	Experimental procedure
1	0	Basal
2	10	Basal
		Coronary stenosis (CS) (20% of basal flow)
3	20	10 min after CS
4	30	20 min after CS
		Administration of enflurane 2.2 Vol %
5	40	30 min after CS (10 min after enflurane)
6	50	40 min after CS (20 min after enflurane)
		End of enflurane
7	60	50 min after CS
8	70	60 min after CS
		Release of coronary stenosis
9	80	10 min after opening of CS
10	90	20 min after opening of CS

TABLE II. *Haemodynamic variables E = enflurane group* (n=9); *C = control animals* (n=5). *MAP = mean aortic pressure; LVEDP = left ventricular end-diastolic pressure, CO = cardiac output; TSR = total peripheral resistance;* $dp/dt_{max}/IP$ = *(Krayenbuehl index; see Methods);* CF_{LAD} = *inflow of the left anterior descending coronary artery; CPP = coronary perfusion pressure* *$P<0.05$; **$P<0.01$, *enflurane group compared with the control dogs for the same time.* †$P<0.05$ *compared with the preconstriction basal value*

		Basal		Coronary stenosis (Flow 20% of basal value)						Basal	
						←— Enflurane —→					
		0 min	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min
Heart rate	E	165±12	166±11	173±31	172±34	165±12	153±11*	153±9**	159±9**	155±9*	153±10*
(beat min^{-1})	C	168±16	165±17	183±8	187±8	192±7	194±8	195±6	199±6	190±7	190±7
MAP	E	112±5	115±5	111±6	113±6	102±8	98±7†	103±6	105±5	107±5	108±6
(mm Hg)	C	95±5	96±5	95±6	93±7	94±6	95±5	94±4	97±4	94±4	95±5
LVEDP	E	4.8±0.7	4.7±0.6	7.2±1.2	7.8±1.5	7.2±1.4	7.4±1.5	5.9±1.0	5.3±0.9	4.9±0.7	5.4±0.6
(mm Hg)	C	3.2±0.8	3.4±0.8	4.6±1.0	4.6±1.0	4.2±1.0	4.0±1.0	4.2±1.2	3.3±1.0	2.4±0 8	2.4±0.8
CO	E	137±13	136±11	126±8	126±14	121±10	118±13	124±11	118±11	124±12	126±10
(ml^{-1} kg min^{-1})	C	123±8	120±9	117±11	111±8	110±8	114±5	121±8	116±10	115±8	114±10
TSR	E	4372±427	4354±356	4710±432	5128±464	4436±435	4436±501†	4272±426	4816±504	4619±425	4597±467
(dyne s^{-1} cm^{-5})	C	3307±348	3409±378	3548±475	3565±364	3715±408	3592±423	3334±405	3630±424	3538±339	3628±421
(dp/dt_{max})/IP	E	31.8±1.5	31.3±2.3	26.8±2.5	26.8±1.4†	25.0±1.6	25.2±1.4	25.8±1.7	25.7±1.5	27.8±1.7	29.2±1.6
(s^{-1})	C	29.4±0.4	30.2±0.8	25.1±1.2	25.7±1.3†	25.2±1.3	25.5±1.5	26.6±1.6	26.8±1.5	29.0±1.5	28.8±1.1
CF_{LAD}	E	39±2	38±3	11±1†	11±1	9±1	10±1	10±1	12±2	51±6	46±6
(ml min^{-1})	C	33±3	34±3	6±1†	7±1	7±1	7±1	6±1	7±1	51±11	42±10
CPP	E	99±5	100±5	96±5	97±6	86±4	81±5†	88±6	92±6	93±5	92±4
(mm Hg)	C	81±4	81±5	79±5	76±5	77±6	78±6	78±5	83±6	80±5	79±6

was a slight, non-significant increase in the heart rate. LVEDP increased slightly in the enflurane group (EG) and in the control group (CG). Contractility (dp/dt_{max}/IP) decreased significantly in both groups (EG by 14%: CG by 17%, $P < 0.05$). Cardiac output was unaffected, and total peripheral resistance (TSR) was unchanged. Coronary perfusion pressure (CPP) decreased slightly in the enflurane group following the stenosis.

The administration of enflurane 2.2 vol.% 20 min after the stenosis (episodes 5 and 6) was followed by effects similar to those described in the literature (Horan et al., 1977; Merin, Kumazawa and Luka, 1976). MAP decreased from 113 ±6 mm Hg by 10% 10 min after enflurane to 102 ± 8 mm Hg, and at episode 6 by 13% to 98 ± 7 mm Hg ($P < 0.05$). Enflurane decreased CPP from 97 ± 6 to 81 ± 5 mm Hg ($P < 0.05$). Heart rate was reduced by a maximum of 11%. The TSR decreased by 14% ($P < 0.05$) during the administration of enflurane. All these values began to increase again after the withdrawal of the enflurane, showing that the effects were reversible.

Enflurane had no detectable effects on the LVEDP. Cardiac output tended to decrease after enflurane in isolated experiments, but the mean reduction was not significant.

Regional function (fig. 2)

A substantial increase in the end-diastolic length (EDL) was recorded 10 min after the stenosis. This was more pronounced in the enflurane group (27%; $P < 0.001$) than in the control group (18%; $P < 0.001$). Segmental shortening (ΔL), as a function of time, decreased significantly following stenosis in both groups ($P < 0.05$). Enflurane caused no decrease in ΔL. Discontinuation of enflurane was followed by an increase which did not occur in the control group at this time.

Myocardial blood flow

Regional myocardial blood flow decreased following the stenosis, especially in the inner layers of the ischaemic area—20% of the baseline value in the CG and 26% in the EG. Although the constriction was

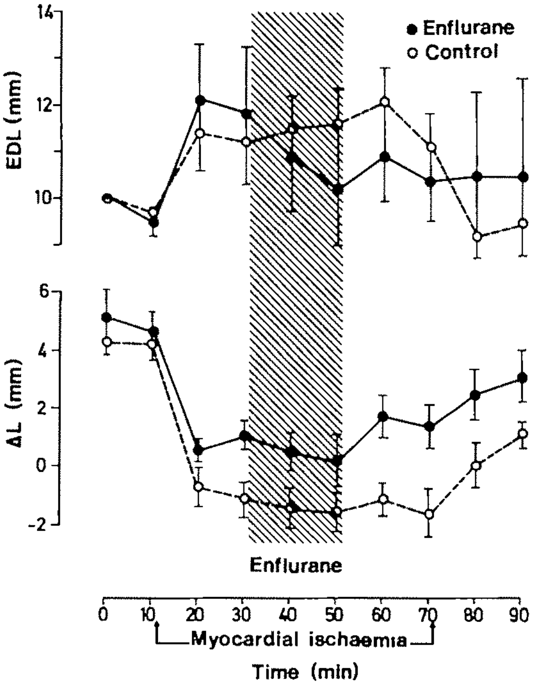

FIG. 2. Regional myocardial function in the ischaemic area. Under enflurane a decrease of the end-diastolic muscle length (EDL) was observed in contrast to the segmental shortening of the muscle fibres (ΔL). Mean values ± SEM.

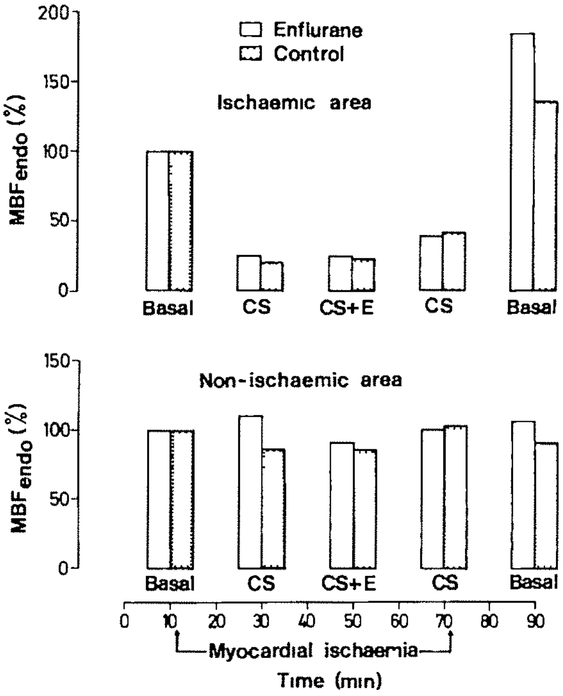

FIG 3. Myocardial blood flow in the subendocardial layers (MBF_{endo}). Changes in percent of basal flow in the ischaemic area of the left anterior coronary artery (LAD) and in the non-ischaemic region of the circumflex coronary artery (CCA). CS = coronary stenosis. CS+E = coronary stenosis + enflurane administration.

TABLE III. *Regional myocardial blood flow (±SEM); ratio of flow in subendocardial layer to that in subepicardial layer. CS = coronary stenosis. CS+ E = coronary stenosis + enflurane administration*

Area	Basal 10 min	CS 30 min	CS + E 50 min	CS 70 min	Basal 90 min
Ischaemic					
E	0.92	0.42	0.41	0.53	1.38
	±0.06	±0.08	±0.07	±0.05	±0.24
C	1.05	0.29	0.56	0.64	1.14
	±0.02	±0.03	±0.16	±0.15	±0.09
Non-ischaemic					
E	1.05	1.05	1.09	1.09	1.13
	±0.04	±0.06	±0.05	±0.07	±0.08
C	1.17	1.08	1.09	1.16	1.13
	±0.08	±0.07	±0.07	±0.08	±0.07

maintained at the same pressure, myocardial blood flow increased in all layers in the course of the experiment, especially in the subendocardial layers (endo), so that at experimental stage 8 (= 60 min after stenosis and 20 min after termination of the enflurane administration), MBF_{endo} in the LAD distribution was only 45% of the baseline value in the CG and 41% in the EG (fig. 3). There was, however, no significant difference between the subendocardial blood flows (MBF_{endo}) in the two groups. The endo/epi ratio was unchanged during the ischaemic period in the LAD distribution, nor was it affected by enflurane (table III).

The coronary vasoconstriction itself had no effect on the endo/epi ratio of the non-stenosed myocardium, that is, the region supplied by the circumflex coronary artery (CCA): there were no significant differences from baseline values.

Myocardial metabolism (fig. 4)

After the onset of coronary stenosis, the normal myocardial lactate extraction was turned into lactate production in both groups. This lactate production decreased significantly after the administration of enflurane ($P < 0.01$). In contrast, in the control group a further discernible increase in lactate production was seen. After the withdrawal of enflurane, lactate extraction did not change, but remained nearly constant. The values in both groups returned to baseline values on release of the stenosis.

There were no changes in any given direction in other metabolic values, for example pyruvate, sodium and potassium concentrations.

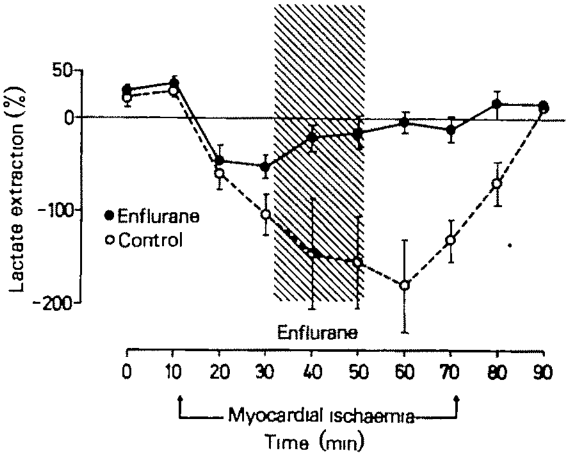

FIG 4. Regional myocardial lactate extraction in control dogs (○) and in the enflurane group (●). After the onset of the coronary stenosis lactate was produced in both groups. Enflurane reduced this lactate production, whereas a marked lactate output from the ischaemic area continued in the control group. Mean values ± SEM.

DISCUSSION

In this study, the effects of enflurane on regional myocardial variables were investigated in dogs in which the heart had been rendered acutely ischaemic.

In both groups, the administration of pentobarbitone 15 mg kg^{-1} caused the well-known increase in heart rate. However, there were no significant differences between the control animals and the enflurane group before exposure to the volatile agent. Following the coronary stenosis, a further but insignificant increase in heart rate occurred (no further increments of pentobarbitone were given during the period of myocardial ischaemia).

The heart rate decreased to basal values during enflurane administration. In contrast, this variable remained increased in the control group. On the other hand, enflurane is known to reduce the total peripheral vascular resistance (Horan et al., 1977; van Ackern et al., 1979). The global contractility, expressed as dp/dt_{max} of the non-constricted left ventricle, was diminished as much in response to enflurane as in the ischaemic area, measured as regional change in contractility, ΔL. This means that, under the influence of enflurane, the non-affected area as well as the ischaemic region contracts with reduced inotropism against a smaller afterload. These reductions in contractility and wall tension must result inevitably in a decrease of the myocardial oxygen consumption unless the myocardial depression is so severe that it causes a compensatory increase in LVEDP. The fact that this did not occur is indicated by the behaviour of the EDL in the ischaemic area, and of the LVEDP in the entire ventricle.

The endocardial flow rates during ischaemia were virtually the same in the two groups, with 21 ml min^{-1}/100 g (EG) and 23 ml min^{-1}/100 g (CG). The perfusion pressure during ischaemia was slightly higher in the enflurane group—but before the actual administration of enflurane—than in the control animals. The perfusion pressure decreased by 16% approximately in the course of the administration of enflurane. There was no change in this variable in the control group. At the end of the enflurane administration, perfusion pressure was 81 mm Hg, being 78 mm Hg in the control group at the same time. There was no difference between the two groups.

Enflurane not only prevented a further increase in lactate production, but it led to a decrease in lactate output. As lactate production did not increase at the end of ischaemia and after withdrawal of enflurane in spite of an increase in MBF, the difference between both groups could not be explained by intracellular or interstitial lactate retention.

It is very difficult to compare the results obtained in different experimental models and under different experimental conditions. Furthermore, authors differ in their interpretations of the term "critical coronary stenosis". Lowenstein and colleagues (1981) found that halothane (between 0.5 and 2.0 vol.%) produced no change in regional myocardial ischaemia. A comparison of the two experimental models shows that Lowenstein and colleagues, according to their own definition of the changes in the regional contraction patterns, used a model of mild ischaemia, whereas our own experiments involved more severe ischaemia. They administered a basal anaesthetic of halothane 0.5 vol.% to their animals, but there was no reference to control values without halothane.

Hickey and co-workers (1980), who like us measured the myocardial blood flow and lactate extraction, found that the administration of halothane at 1.2–2.1 MAC to dogs with 75% coronary stenosis resulted in severe reductions in endocardial blood flow and lactate production. However, the low diastolic aortic pressure of 42 mm Hg these authors reported would probably prevent a beneficial effect. This may also be the case in the study by Behrenbeck and associates (1980) who carried out a canine study with coronary artery stenosis of approximately 80%. They reported that the administration of 0.5–1.5 MAC of halothane resulted in a significant decrease in the systolic change in wall thickness in the ischaemic area, as an expression of an increase in ischaemia. They attributed the increase in ischaemia to peripheral circulatory effects and to the global depression induced by halothane.

Verrier and colleagues (1980), who also designed a study with coronary stenosis, reported that the administration of halothane 0.8 vol.% to dogs with a low mean aortic pressure of 89 or 84 mm Hg was followed by a reduction in myocardial oxygen consumption and an increase in coronary reserves, but these advantages of halothane were lost when the heart rate was maintained constant by electrical pacing. In our study, however, enflurane did not cause a significant decrease in the heart rate and so a decrease in heart rate was not responsible for the beneficial effects of enflurane.

In conclusion, our study in dogs showed that enflurane may be advantageous during severe myocardial ischaemia. This is indicated by the reduced regional contraction, measured as EDL and ΔL, the unchanged subendocardial blood flow, and the improved lactate extraction in the ischaemic area.

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EFFECT OF PROPOFOL, THIOPENTONE AND ETOMIDATE ON ADRENAL STEROIDOGENESIS *IN VITRO*

A. LAMBERT, R. MITCHELL AND W. R. ROBERTSON

SUMMARY

The i.v. anaesthetic agents propofol, thiopentone and etomidate inhibited ACTH-stimulated production of cortisol by guineapig dispersed adrenal cells in a dose-related manner. For two of the drugs, propofol and thiopentone, inhibition occurred over a similar concentration range: 2×10^{-5} – 5×10^{-4} *mol litre*$^{-1}$*. With etomidate, inhibition occurred over a much lower concentration range* (5×10^{-8} – 5×10^{-6} *mol litre*$^{-1}$)*. The concentrations of anaesthetic which induced 50% inhibition of cortisol secretion were propofol* 1.7×10^{-4}*, thiopentone* 1.6×10^{-4}*, and etomidate* 1.0×10^{-7} *mol litre*$^{-1}$*.*

Etomidate, a carboxylated derivative of imidazole, is a rapidly acting hypnotic drug which is administered i.v. either as a bolus or by continuous infusion, to produce anaesthesia. It is known to inhibit adrenal steroidogenesis *in vivo* (Allolio et al., 1983; Fellows, Bryne and Allison, 1983) and *in vitro* (Lambert et al., 1983; Lambert, Frost et al., 1984; Lee Wagner et al., 1984), and has been implicated in the increase in mortality found in multiply-injured patients (Ledingham and Watt, 1983). As a result, etomidate has been the object of considerable attention in the past year (Owen and Spence, 1984). The association between etomidate and adrenocortical suppression prompted us to investigate two further i.v. anaesthetic agents for possible anti-adrenal effects. The first, thiopentone, a short-acting barbiturate, has been used frequently for the induction and, on occasion, the maintenance of anaesthesia since its introduction in 1934 (Dundee and Wyant, 1974). The second drug, propofol (diisopropylphenol, Diprivan), is a relatively new anaesthetic first described in 1977 (Kay and Rolly, 1977). It is a rapidly acting agent which is suitable for anaesthesia of short duration or for prolonged anaesthesia when administered as a continuous infusion.

MATERIALS AND METHODS

The method used for the preparation of isolated guineapig adrenal cells has been described in detail elsewhere (Lambert and Robertson, 1982; Lambert, Garner et al., 1984). Briefly, the adrenals from two male guineapigs were chopped into 1-mm cubes using a McIlwain tissue chopper, the tissue pieces washed with Eagle's minimum essential medium (EMEM) and dispersed by mechanical agitation in EMEM containing collagenase 2 mg ml^{-1}. The cells were collected by centrifugation (300 *g* for 5 min) and washed twice with Eagle's medium containing 0.5% bovine serum albumin (BSA), calcium 8 mmol litre^{-1} and ascorbate 2 mmol litre^{-1}. The above mixture served as incubation medium. Finally, the cell suspension was filtered through nylon 100-μm mesh. The cells (1×10^6 cells ml^{-1}) were then pre-incubated for 2 h at 37 °C in an atmosphere of 100% oxygen. After preincubation, the cell suspension was centrifuged to remove any secreted cortisol and resuspended in fresh incubation medium.

In all experiments, 40-μlitre aliquots of cell suspension were dispensed into a 96-well tissue culture plate and stimulated for 90 min at 37 °C with ACTH (1–24) 50 ng litre^{-1} either alone or in combination with increasing concentrations of the anaesthetic. The anaesthetics were incorporated into cell suspension in dimethylsulphoxide (DMSO) such that the final concentration of solvent was 2.5%. In some experiments thiopentone was incorporated into the

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cell suspension in aqueous medium (EMEM). When appropriate, 2.5% DMSO was also included in the basal (no added ACTH) and ACTH 50 ng litre^{-1}-stimulated wells. The total volume of incubate in each well was 80 μlitre and the final cell concentration was 0.75 × 10^6 cells ml^{-1}. After 90 min incubation, duplicate 10-μlitre samples were taken and assayed for cortisol by specific radioimmunoassay (Amerlex kit, Amersham International, U.K.). None of the anaesthetic agents interfered with the radioimmunoassay at the concentrations used.

Statistical analysis of results

In each experiment, duplicate wells were set up containing no added ACTH (basal) and ACTH 50 ng litre^{-1} in the absence of drug. Single wells were set up at each drug concentration. Duplicate samples were taken from each well. Intra- and inter-well coefficients of variation for this system are <6 and <10%, respectively (n > 100 in both cases) (Lambert, Garner et al., 1984). Levels of significance were estimated by Student's t test.

Source of chemicals

ACTH (1–24) (Synacthen) was a gift from Dr C. McMartin (Ciba–Geigy, Horsham, West Sussex). Propofol (Diprivan) was supplied by ICI Pharmaceuticals, Macclesfield, Cheshire and thiopentone by May and Baker Ltd, Dagenham. Etomidate was obtained from Janssen Pharmaceuticals, Marlow, Bucks. DMSO was purchased from Fisons Ltd, Loughborough.

RESULTS

The effects of increasing concentrations of propofol, thiopentone and etomidate on ACTH 50 ng litre^{-1}-stimulated cortisol secretion are shown in figure 1. For two of the anaesthetics (etomidate and propofol) the composition of the medium was 97.5% EMEM–2.5% DMSO, and in this medium ACTH 50 ng litre^{-1} provoked a 21 ± 4-fold (mean ± SD, n = 12) increase in cortisol secretion over the control. Inhibition of cortisol secretion by etomidate and propofol occurred over the ranges 5 × 10^{-5} to 5 × 10^{-6} and 2 × 10^{-5} to 5 × 10^{-4} mol litre^{-1}, respectively. In the case of thiopentone, the maximum solubility of this drug in a 97.5% EMEM–2.5% DMSO mixture is 1.25 × 10^{-4} mol litre^{-1} and this concentration gave rise to only 34% inhibition of cortisol secretion. In 100% EMEM the limit of solubility was

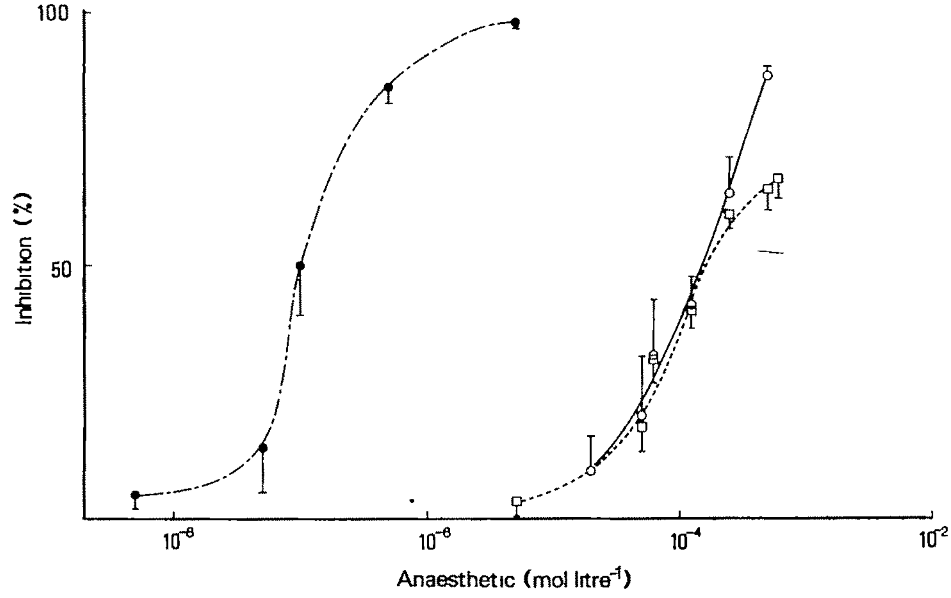

FIG 1. Inhibition of ACTH 50 ng litre^{-1}-stimulated cortisol secretion by etomidate (●), propofol (□) and thiopentone (○). Propofol and etomidate were incorporated into the cell suspension in DMSO such that the final concentration of solvent was 2.5%; thiopentone was incorporated in aqueous medium. When appropriate, 2.5% DMSO was also included in the basal (no added ACTH) and ACTH 50 ng litre^{-1}-stimulated wells. Results are mean ± SD (n = 6; each experimental point was performed in duplicate and the experiment was repeated three times).

TABLE I. *Plasma concentrations 1 min after injection of an induction dose of etomidate, thiopentone or propofol. †Recalculated in mol litre^{-1}*

Anaesthetic	Induction dose (mg kg^{-1})	Plasma concentration† 1 min after injection (mol litre^{-1})	Reference
Etomidate	0.3	$4.6–5.7 \times 10^{-6}$	Doenicke and others (1972)
Thiopentone	6.0	1.3×10^{-4}	Burch and Stanski (1983)
Propofol	1.3	$2.2–4.5 \times 10^{-5}$	Adam, Kay and Douglas (1982)

increased to 5×10^{-4} mol litre^{-1} and this concentration resulted in 87% inhibition. Over the thiopentone concentrations where comparison could be made (5×10^{-6} to 1.25×10^{-4} mol litre^{-1}) there were no significant differences in the degrees of inhibition observed in the two media. For example, with thiopentone 1.25×10^{-4} mol litre^{-1} the degrees of inhibition in 97.5% EMEM–2.5% DMSO and 100% EMEM were 37 ± 3 and 42 ± 6% (mean ± SD, $n = 6$), respectively, and with 5×10^{-5} mol litre^{-1}, inhibitions were 20 ± 8 and 20 ± 12% ($n = 6$), respectively. The inhibition plot for thiopentone shown in figure 1 is over the extended concentration range up to 5×10^{-4} mol litre^{-1} in 100% EMEM. The concentration of anaesthetic which provoked 50% inhibition of cortisol secretion was (mean ± SD, $n = 3$ experiments) $1.6 \pm 0.3 \times 10^{-4}$, $1.7 \pm 0.3 \times 10^{-4}$ and $1.0 \pm 0.1 \times 10^{-7}$ mol litre^{-1} for thiopentone, propofol and etomidate, respectively.

DISCUSSION

Direct anti-adrenal steroidogenic effects have been demonstrated for the first time for the anaesthetic agents propofol and thiopentone using an *in vitro* approach based upon dispersed guineapig adrenal cells (Lambert et al., 1983; Lambert, Ratcliffe and Robertson, 1984; Lambert et al., 1985). The ED_{50} values recorded for inhibition of ACTH-stimulated cortisol secretion by these two drugs were similar (1.7 and 1.6×10^{-4} mol litre^{-1}, respectively). In contrast, etomidate, an anaesthetic now known to block adrenal steroidogenesis *in vivo* (Allolio et al., 1983; Fellows, Byrne and Allison, 1983; Lee Wagner et al., 1984) was approximately 1500–1600 times more potent as an adrenal inhibitor *in vitro*, having an ED_{50} of 1.0×10^{-7} mol litre^{-1}, a figure in excellent agreement with our earlier reports (Lambert et al., 1983; Lambert, Ratcliffe and Robertson, 1984).

In general, the relevance of the relative anti-adrenal steroidogenic potency measured in any *in vitro* system to its pharmacological effects *in vivo* must be viewed with some caution. However, this does not mean they give no indication as to possible *in vivo* activity and it can be seen (table I) that the concentration of etomidate found in plasma 1 min after administration of an induction dose to human subjects greatly exceeds (>50 times) its *in vitro* ED_{50} value. In contrast, thiopentone, an anaesthetic for which there is no clinical evidence of adrenal inhibition, may achieve plasma concentrations which can only approach its ED_{50}. Moreover, an induction dose of propofol leads to a 1-min plasma concentration of 4.5×10^{-5} mol litre^{-1}, a concentration which would lead to <20% inhibition of adrenal steroidogenesis in our *in vitro* assay. On this basis, and in the absence of any clinical or other evidence from animal studies, it is unlikely that these two drugs have any short-term deleterious effects on the steroidogenic function of the adrenal gland *in vivo*.

In conclusion, we have demonstrated that propofol and thiopentone are relatively weak inhibitors of adrenal steroidogenesis *in vitro*. Furthermore, we have confirmed that etomidate is a potent inhibitor of adrenal function, a characteristic it shares with ketoconazole, another structurally related substituted imidazole drug (Pont et al., 1982; Loose et al., 1983).

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COMPARISON OF THE EFFECTS OF ETOMIDATE, THIOPENTONE AND PROPOFOL ON CORTISOL SYNTHESIS

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SUMMARY

The inhibitory effects of etomidate, thiopentone and propofol on basal and ACTH-stimulated cortisol synthesis by isolated bovine adrenocortical cells have been examined. Concentrations required for 50% inhibition of ACTH-stimulated cortisol output were 1.1 × 10^{-4} mol $litre^{-1}$ for propofol, 3 × 10^{-5} mol $litre^{-1}$ for thiopentone and 4.6 × 10^{-7} mol $litre^{-1}$ for etomidate. At concentrations likely to be achieved during anaesthesia, etomidate would block cortisol output by isolated cells, thiopentone might slightly reduce output and propofol would be unlikely to alter cortisol synthesis significantly.

Following the initial observations of Ledingham and Watt (1983) of increased mortality among patients in the intensive care unit who were sedated with etomidate, the inhibitory side-effects of this hypnotic on adrenal steroidogenesis have been confirmed (Lambert et al., 1983; Fraser et al., 1984; Kenyon et al., 1984). However, a recent editorial in this journal has drawn attention to inconsistencies of plasma cortisol concentrations in studies which have compared the effects of bolus injections of thiopentone and etomidate (Owen and Spence, 1984). Although our own comparative studies and those of Sebel, Verghese and Makin (1983) showed no significant difference between the effects of etomidate and thiopentone on plasma cortisol concentration, etomidate caused an increase in the concentration of deoxycorticosterone (Duthie, Fraser and Nimmo, 1984), which was consistent with its known inhibition of the adrenal 11β-hydroxylase enzyme (Fraser et al., 1984; Fry and Griffiths, 1984; Kenyon et al., 1984; Wagner et al. 1984). Since thiopentone-treated patients had normal deoxycorticosterone concentrations, but cortisol concentrations similar to those in patients treated with etomidate, it may be that thiopentone also decreases cortisol synthesis, but by a different mechanism. Accordingly, the present study has compared the effects of etomidate and thiopentone on cortisol biosynthesis *in vitro*. In addition, we have tested propofol (2, 6-diisopropylphenol: ICI 35 868), a new drug the pharmacokinetic properties of which suggest it might be suitable for the maintenance of anaesthesia when given by i.v. infusion (Glen and Hunter, 1984).

MATERIALS AND METHODS

Cells were isolated from minced slices of the inner adrenal cortex of bovine adrenals by collegenase digestion and incubated in medium 199 as previously described (Kenyon et al., 1984). Aliquots of cell suspension (100 μlitre) were added to 400 μlitre of incubation medium with and without ACTH 10^{-9} mol $litre^{-1}$ (Synacthen, Ciba–Geigy) and with various concentrations of one of the three anaesthetics. Etomidate (Janssen Pharmaceuticals) was dissolved in propylene glycol and added to the 400-μlitre incubation medium to give final concentrations of 0 (vehicle alone), 1.6, 8, 40, 200 and 1000 ng ml^{-1}.

Sodium thiopentone (May and Baker) was dissolved in medium 199 to give final concentrations of 0, 0.08, 0.4, 2, 10 and 50 μg ml^{-1}. Propofol (ICI) was diluted with intralipid (ICI) and added to medium 199 to give final concentrations of 0 (vehicle alone), 0.04, 0.2, 1, 5 and 25 μg ml^{-1}. Incubations were carried out in sextuplicate for 1 h at 37 °C in 95% oxygen: 5% carbon dioxide. Cortisol concentration in

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the supernatant was measured by radioimmunoassay. Unpaired *t* tests were used to compare values.

RESULTS

All three drugs inhibited cortisol synthesis by ACTH-stimulated cells (fig. 1). Etomidate 8 ng ml^{-1} (3.3 × 10^{-8} mol litre^{-1}) slightly but significantly increased ACTH-stimulated cortisol synthesis compared with controls treated with vehicle alone ($P < 0.01$), but at 200 ng ml^{-1} had abolished the effects of ACTH compared with controls and had decreased basal synthesis by 80% ($P < 0.001$). Thiopentone was much less potent: 10 and 50 μg ml^{-1} (3.8 × 10^{-5} and 1.9 × 10^{-4} mol litre^{-1}) reduced ACTH-stimulated output by 30% and 85% and basal synthesis by 70% and 85%, respectively. Propofol at all doses appeared to decrease basal cortisol synthesis ($P < 0.001$), although the effect did not appear to be dose-related. ACTH-stimulated synthesis was inhibited by 40% ($P < 0.001$) by propofol 25 ng ml^{-1} (1.4 × 10^{-4} mol litre^{-1}).

Concentrations of anaesthetic required for 50% inhibition of ACTH-stimulated output compared with controls were 1.1 × 10^{-4} mol litre^{-1} for propofol, 3 × 10^{-5} mol litre^{-1} for thiopentone and 4.6 × 10^{-7} mol litre^{-1} for etomidate.

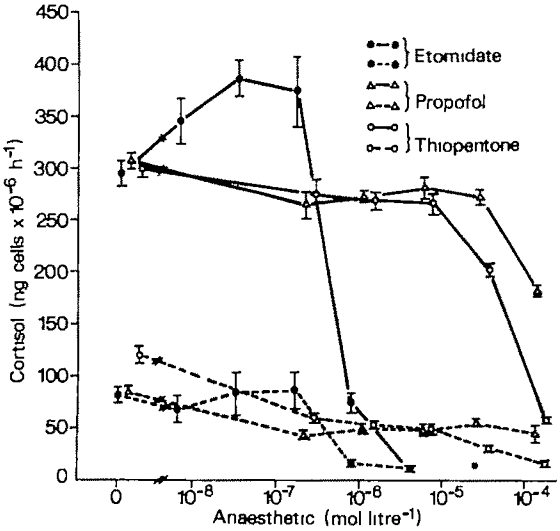

FIG 1. The dose-related effects of etomidate, propofol and thiopentone on adrenocortical function. Values shown are means (± SEM, $n = 6$) of measurements of cortisol biosynthesis by isolated bovine adrenocortical cells incubated with (solid line) and without (broken line) ACTH 10^{-9} mol litre^{-1}, and with various concentrations of anaesthetic.

DISCUSSION

At plasma concentrations which are considered necessary for anaesthesia—8.5 × 10^{-6} mol litre^{-1} for propofol (Adam, Kay and Douglas, 1982), 1.5 × 10^{-5} mol litre^{-1} for thiopentone (Homer and Stanski, 1983 and 4.6 × 10^{-7} mol litre^{-1} for etomidate (Fragen et al., 1983), the degrees of inhibition of ACTH-stimulated cortisol synthesis in the present system would be 12%, 39% and 100%, respectively. Thus, only etomidate is likely to affect steroidogenesis significantly under conditions of normal use.

Etomidate probably inhibits the mitochondrial, cytochrome P450-dependent, 11β-hydroxylase step in the biosynthetic pathway of cortisol (Fraser et al., 1984; Kenyon et al., 1984; Wagner et al., 1984). Barbiturates such as thiopentone are known to bind to hepatic cytochrome P450, thereby inhibiting certain steroid metabolizing enzymes (Harvey, 1975). A general inhibition of adrenal cytochrome P450 systems by thiopentone, as opposed to the specific effects of etomidate, would explain the inhibition of cortisol synthesis by thiopentone in the present experiments and also why etomidate, but not thiopentone, increased deoxycorticosterone concentrations in man (Duthie, Fraser and Nimmo, 1984).

Substituted phenols like propofol have not been shown to interfere with steroid metabolism. The slight decrease in ACTH-stimulated cortisol synthesis by propofol at supra-pharmacological concentrations is most likely to be a non-specific toxic effect on the adrenal cell. On the basis of these effects on *in vitro* cortisol biosynthesis, the clinical use of propofol should not be accompanied by the sort of steroidogenic problems seen with etomidate.

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ENZYME INHIBITION BY STEROID ANAESTHETIC AGENTS DERIVED FROM PROGESTERONE

P. BANKS AND C. B. PEACE

SUMMARY

The anaesthetic potency of steroids related by metabolism to progesterone shows marked variation with small changes in structure. In addition, the same group of substances have varying abilities to inhibit bacterial luciferase competitively, although there is no correlation between anaesthetic and inhibition potency. The data do, however, show that closely related hydrophobic steroids are able to interfere with the catalytic activity of an enzyme selectively and, by inference, suggest that differences in anaesthetic potency could be a consequence of selective differences in ability to interact with a target protein.

General anaesthesia can be induced by such a variety of molecules that attempts to formulate an all-embracing hypothesis concerning their mode of action are unlikely to be successful. While non-specific perturbations of phospholipid bilayers or of membrane proteins may be the primary cause of the anaesthesia produced by some agents, it is equally possible that, in other instances, a specific interaction between one or more proteins and the anaesthetic is the initial event (Richards, 1978; Richards et al., 1980; Halsey, Green and Wardley-Smith, 1980). Steroid anaesthetics probably fall into this second category, since the potencies of closely related molecules can differ greatly (Selye, 1941, 1942; Phillipps, 1974). The purpose of this paper is to demonstrate that a group of naturally occurring steroids, formed by the reduction of progesterone, not only have markedly different anaesthetic potencies, but also differ in their ability to inhibit a soluble enzyme with a hydrophobic substrate-binding site.

MATERIALS AND METHODS

Dose–response curves for anaesthetics

The steroids were taken up in a solution of propyleneglycol and acetone (15:2 v/v) and mixed with a vortex shaker for 5 min as physiological saline (0.9% sodium chloride) was added to give a final mixture of propyleneglycol, acetone and saline of 15:2:5 (v/v). The solution was then heated at 50 °C under reduced pressure for 30 min to remove the acetone. For each dose of anaesthetic, each member of a group of five adult mice (around 25 g) was injected with 0.1 ml of steroid-containing solution via the tail vein. Induction of anaesthesia was judged by failure of the righting reflex and of the withdrawal response to pinching a rear foot. Injection of vehicle alone had no anaesthetic effect.

Light production by bacterial luciferase

A tube containing 1.3 ml of phosphate buffer 0.1 mol litre^{-1}, pH 6.8; 0.1% mercaptoethanol 0.1 ml; 0.2 ml of luciferase 10 mg ml^{-1} in phosphate buffer; 0.2 ml of NADH 10 mg ml^{-1}; 0.2 ml of FMN 0.2 mg ml^{-1} and 0.05% methanol ± steroid was placed in the cell housing of a Farand fluorimeter without secondary filters and with the light source switched off. Then 0.05 ml of decaldehyde 1 mg ml^{-1} in methanol was injected from a syringe, the needle of which passed through the lid of the cell housing. The instantaneous light output was recorded in arbitrary units on a Servoscribe recorder.

Chemicals

All steroids, decaldehyde and bacterial luciferase Type V were obtained from Sigma Chemical Co. Propyleneglycol was from British Drug Houses Ltd.

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TABLE I. *Anaesthetic potencies of steroids related to progesterone. Mice were injected with steroid via the tail vein as described under Materials and Methods. AD_{25} and AD_{50} are the doses anaesthetising 25 and 50% of mice respectively*

Steroid	AD_{25} (mg kg^{-1})	AD_{50} (mg kg^{-1})
5β-Pregnan 3α-ol, 20-one	1.5	2.0
5α-Pregnan 3α-ol, 20-one	2.6	5.4
5β-Pregnan 3, 20-dione	9.2	13.8
5α-Pregnan 3, 20-dione	16.0	22.5
5α-Pregnan 3β-ol, 20-one	21.2	> 40.0
5β-Pregnan 3β-ol, 20-one	46.5	> 70.0
Progesterone	51.0	> 60.0
5β Pregnan 3α, 20α-diol	No effect	No effect

RESULTS

Table I shows that the anaesthetic potencies of progesterone and various of its derivatives differ greatly; especially noteworthy is the marked effect of converting the 20-oxo group into an alcohol. Figure 1 shows that the potent anaesthetic 5β-pregnan 3α-ol, 20-one is able to inhibit bacterial luciferase competitively whilst the corresponding, non-anaesthetic diol (5β-pregnan 3α-ol, 20α-ol) does not.

Table II demonstrates that 5α pregnan derivatives which are anaesthetics fail to inhibit luciferase, while the anaesthetic 5β derivatives are inhibitors. The diols, which are inactive as anaesthetics, also fail to inhibit the enzyme.

DISCUSSION

TABLE II. *Inhibitory activity of steroids related to progesterone on light production by luciferase. Steroids were added in methanol 0.5ml, and methanol 0.5 ml was present in the drug-free control*

Steroid (6 × 10^{-5} mol litre^{-1})	Light production (% of control) Range	*n*
None	95.0–105.0	3
5β-Pregnan 3α-ol, 20-one	63.3– 66.6	4
5β-Pregnan 3, 20-dione	57.4– 71.3	3
5β-Pregnan 3β-ol, 20-one	67.3– 66.3	2
5β-Pregnan 3α-ol, 20α-ol,	93.6–102.5	3
5β-Pregnan 3α-ol, 20β-ol	101.2–105.1	2
5α-Pregnan 3α-ol, 20-one	91.0– 96 1	2
5α-Pregnan 3β-ol, 20-one	98.7–103.8	2
Progesterone	49.5– 58.4	2

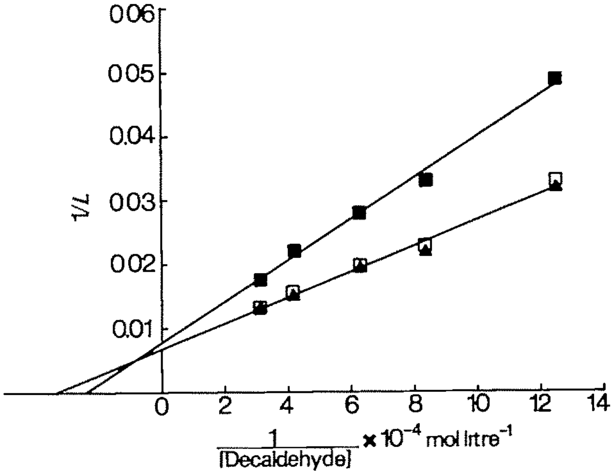

FIG. 1. Lineweaver–Burk plot: inhibition of light emission. With decaldehyde as substrate (▲); *K*m = 2.8 × 10^{-5} mol litre^{-1}; L_{max} = 139 units. In the presence of 5β-Pregnan 3α-ol, 20-one 6 × 10^{-5} mol litre^{-1} (■), Km_{app} = 4.3 × 10^{-5} mol litre^{-1} and L_{max} = 135 units; K_I for 5β-Pregnan 3α-ol, 20-one = 5.5 × 10^{-5} mol litre^{-1}. In the presence of 5β-Pregnan 3α-ol, 20α-ol 6 × 10^{-1} mol litre^{-1} (□), *K*m and L_{max} were the same as the control values. The curves were fitted by linear regression analysis.

Correlation between anaesthetic potency and lipid solubility, together with a lack of any obvious chemical similarity between anaesthetics, led to attention being focused on interactions between anaesthetics and the lipid components of membranes. However, experiments on cell-free extracts and purified luciferase showed that the ability of simple anaesthetics to extinguish the light production by cultures of luminous bacteria (Halsey and Smith, 1970; White and Dundas, 1970) could not be ascribed to an interaction with the cell membrane, but resulted from a direct effect on the enzyme concerned (Middleton and Smith, 1976). The present paper demonstrates that some anaesthetic steroids are able to act as inhibitors of luciferase, that others are not and that some closely related molecules are inactive in both respects. It is apparent that relatively small changes in structure which would not be expected to alter the purely physical properties of the molecules greatly can, nevertheless, cause marked changes in anaesthetic or inhibitor potency, or both. This, in turn, suggests that such molecules can engage in specific interactions with proteins and that, by inference, suitable steroids could bind specifically to membrane-bound enzymes, receptors or transporters to induce anaesthesia. Such interactions need not, of course, be at the active site as with luciferase, but could be at any site on a protein the occupancy of which leads to a functional change.

Progesterone, for example, has been shown to inhibit adenyl cyclase by affecting the regulatory G/F subunit (Sadler and Maller, 1981). Whether that effect is directly on the protein or involves perturbation of adjacent lipid structures in the membrane remains to be seen.

The reductive metabolism of progesterone, itself a moderately potent anaesthetic, yields a set of 5α and 5β pregnan diones and 3-ol, 20-ones which are very potent general anaesthetics. Further reduction to the corresponding diols causes a loss of these anaesthetic properties (Phillipps, 1974). The presence of enzymes in the brain able to carry out activating transformations (Martini, 1978) raises the possibility that some reduced derivatives of progesterone may exert a modulating influence on neurones under physiological conditions, especially during pregnancy when progesterone concentrations are increased.

Since this work was completed, Franks and Lieb (1984) have provided evidence that a range of anaesthetics are able to act competitively against the substrate luciferin to inhibit luciferase from the firefly *Photinus pyralis*. These studies led their authors to conclude that general anaesthetics, despite their chemical and structural diversity, act by competing with endogenous ligands for binding to specific receptors.

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EFFECTS OF SPINAL BLOCKADE WITH BUPIVACAINE ON PARTURITION IN RATS

D. F. LI, M. BAHAR AND M. ROSEN

SUMMARY

On the day of expected delivery, primigravid rats received 0.5% bupivacaine continuously through a chronically implanted intrathecal cannula to produce intense sensory and motor blockade below the T10 level. The mean duration of delivery was prolonged to 3.1 h compared with 1.4 h in a control group without intrathecal blockade and a group which received an intrathecal infusion of Hartmann's solution. The mean percentages of live births per litter surviving the first 6 h was 94% in the control groups and 42% in those receiving bupivacaine by intrathecal infusion. No increased perinatal mortality was observed in another control group receiving an i.p. infusion of 0.5% bupivacaine in the same dose as that given intrathecally. Two mother rats died during delivery under spinal blockade because of prolonged labour. It is concluded that, without obstetric intervention, intense sensory and motor blockade delayed parturition and increased fetal mortality in the pregnant rats.

Extradural analgesia is widely practised for pain relief in labour. The effects on the duration of the second stage of labour and the incidence of forceps delivery are currently controversial (O'Driscoll, 1975; Studd et al., 1980; Bailey and Howard, 1983; Maresh, Choong and Beard, 1983; Walton and Reynolds, 1984). It is difficult to study the problem in controlled conditions because the second stage of labour is difficult to define and clinical conditions vary widely (Beard and Maresh, 1983; Crawford, 1983; Friedman, 1983; Myerscough, 1983). Immediate operative delivery may be necessary for the sake of actual or suspected fetal compromise. The present study simulated the clinical situation in pregnant rats with the objective of observing the effects of differential degrees of motor and sensory blockade on the parturition process.

MATERIALS AND METHODS

Primigravid Wistar rats (weight 180–220 g before pregnancy) were used. Female rats were mated separately with a fixed stock of experienced males to achieve a good conception rate and to minimize genetic variability of the pups. Conception was calculated from the date when pink vaginal plugs were observed to drop on the collecting trays, at which time the female rats were placed in separate maternity cages until delivery.

On the 16–18th day of gestation (normal gestational period in rats is 21 ± 1 days), rats were anaesthetized with 2.5% halothane in oxygen 0.2 litre min^{-1} via a loose-fitting, cone-shaped mask and the intrathecal space was cannulated with a fine polyethylene catheter in the lumbar region, using a microsurgical technique (Bahar, Rosen and Vickers, 1984). The free end of the catheter was tunnelled under the skin to emerge at the nape of the neck between the ears. The rats recovered in 30 min and no maternal mortality nor premature delivery was observed. The lumbar location of the catheter was verified by injecting 2% lignocaine solution 35 μlitre through the catheter, which invariably resulted in paralysis of both hind limbs and produced analgesia below the lumbar region as tested by applying a haemostat (Yaksh and Rudy, 1977).

Preliminary studies with non-pregnant rats of the same weight showed that a continuous intrathecal infusion of 0.5% bupivacaine 100 μl h^{-1} would

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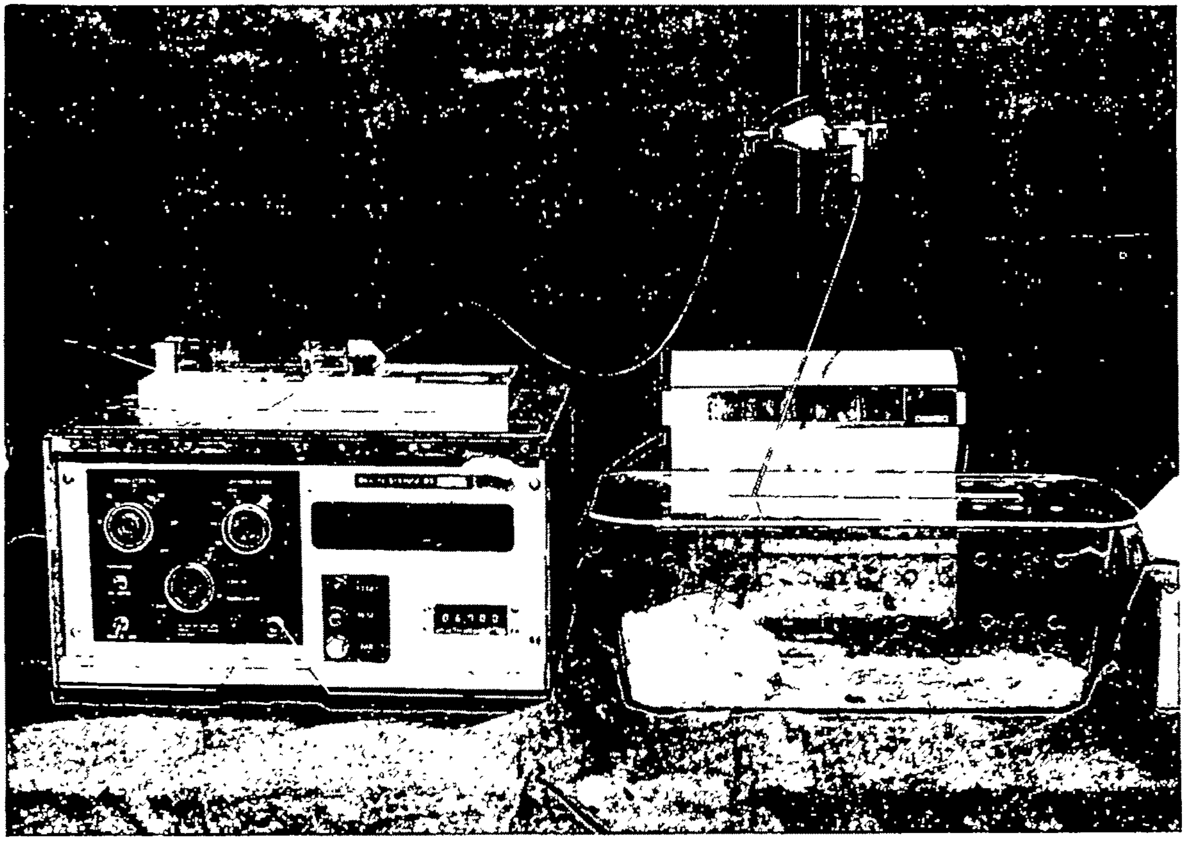

FIG 1. Apparatus for the intrathecal infusion in the rat. On the left was a syringe pump, and a clock was behind the cage. Food and water were on the right side of the cage.

paralyse both hind limbs and result in sensory analgesia to T10 with steady block and without marked fluctuation of analgesic level. The rats still had mobile forelimbs and could reach food and water.

Five rats were randomly allocated to each of the following groups:

(1) Control group with neither jacket nor infusion.

(2) Control group with only jacket and swivel but no infusion.

(3) Intrathecal infusion of Hartmann's solution 100 µl h^{-1}.

(4) Intrathecal infusion of 0.5% bupivacaine 100 µl h^{-1}.

(5) Intraperitonal infusion of 0.5% bupivacaine 100 µl h^{-1}.

On the morning of the expected date of confinement, a small jacket was put on the pregnant rats of groups 2–5 and the spinal catheter was connected to an infusion pump through a flexible metal tether and swivel clamped above the cage (Harvard apparatus) (fig. 1). The appropriate infusion was commenced, in groups 3–5. All rats were then left undisturbed in a quiet, well-lit room until after delivery.

The delivery process was monitored by a video camera and by frequent observations at a distance. The time taken from the appearance of the first pup at the introitus to the completion of delivery of the last pup was recorded as the total duration of delivery. The number of pups delivered and the percentages of liveborn per litter surviving the first 6 h were also recorded. The level of sensory blockade was checked. Results were analysed with Student's *t* test, Chi-square test and analysis of variance.

RESULTS

Pregnant rats delivered quite normally under the experimental conditions. Putting on a jacket and

TABLE I. *Duration of delivery with or without intrathecal blockade (mean ± SD). i.t. = Intrathecal infusion; i.p. = intraperitoneal infusion. No significant differences between the five groups:* † $P = 0.07$; ‡ $P = 0.85$. *Significant difference from group 1 (control):* **$P < 0.001$, ***$P < 0.0001$

	No of pups per litter†	Duration of delivery (h)	Delivery time per pup (min)	Duration of infusion to delivery‡ (h)
Group 1 Control, no jacket no infusion	10.4±1.5	1.3±0.1	7.4±1.1	—
Group 2 Control, with jacket no infusion	9.0±1.0	1.4±0.4	8.9±1.9	—
Group 3 Control, Hartmann's infusion 100 µl h^{-1} i.t.	10.8±1.3	1.4±0.2	7.1±2.1	10.3±8.5
Group 4 0.5% Bupivacaine infusion 100 µl h^{-1} i.t.	9.6±1.1	3.1±1.1**	19.2±6.4***	11.6±6.8
Group 5 0.5% Bupivacaine infusion 100 µl h^{-1} i.p.	11.4±1.5	1.4±0.1	7.6±1.2	13.4±10.0

connecting to a swivel did not interfere with the process of parturition (table I). The mean number of pups per litter was not significantly different ($P=0.07$) in the five study groups. The presentation of the pups was either cephalic or breech at random, and at no time was there an observed difference in the manner of delivery of either presentation.

The delivery time was almost three times longer in the group receiving intrathecal blockade with 0.5% bupivacaine: both the total duration of delivery ($P<0.001$) and the delivery time per pup were significantly prolonged ($P<0.0001$). Observations during the experimental period revealed that this delay was caused by increased intervals between each birth as a result of lack of active maternal effort: normally the mother pulls the baby out with her mouth, but under spinal blockade this did not occur.

In the three control groups, the mean percentages of live births per litter surviving the first 6 h varied between 94% and 96% (fig. 2). In the group receiving spinal blockade, the corresponding figure was only 42% ($P < 0.001$). The group which received the same dose of 0.5% bupivacaine infusion, but by the intraperitoneal route, had a mean percentage of live births per litter of 93%, not significantly different from the control groups.

Intrathecal infusion of Hartmann's solution did not have any motor or sensory effects on the rats. This was also evident from the normal delivery time and normal perinatal mortality when compared with the control group. In the group receiving spinal blockade with bupivacaine, two mother rats died during infusion without delivering the pups. On postmortem examination, the vagina in both rats was distended, with partial extrusion of the fetal head at the introitus. There was no rupture of uterus nor any internal bleeding. The cause of death was attributed to prolonged labour in both cases.

DISCUSSION

Finding a suitable clinical model in which to study the effects of motor and sensory blockade in labour is difficult because of the numerous variables involved.

The effects of spinal morphine on parturition in rats have been reported using the nesting behaviour of the mother to mark the onset of labour (Yaksh et al., 1979). Experience in this study, however,

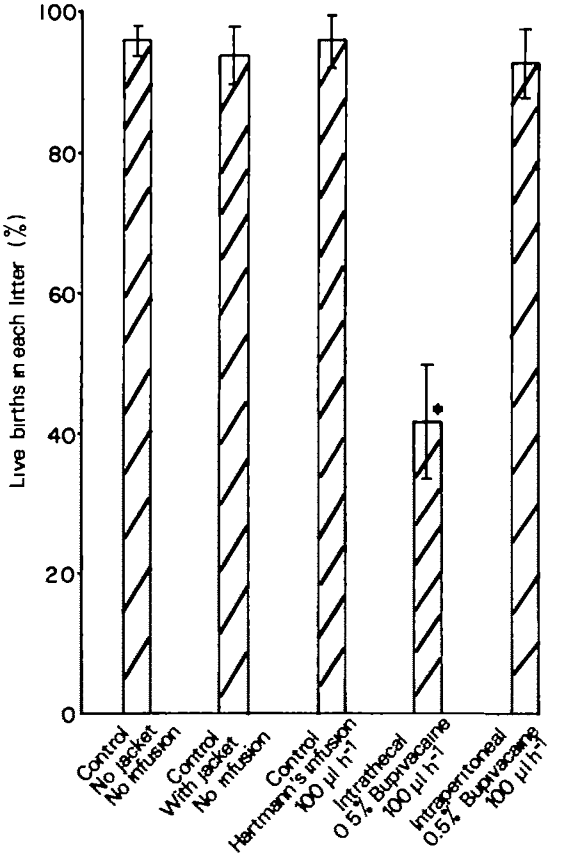

FIG. 2. Mean percentages with standard error of live births in each litter surviving the first 6 h after delivery. *$P < 0.001$.

showed that nesting was not a reliable sign because it was sometimes present 2 days before the day of delivery; instead, the total delivery time was measured from appearance of the first pup at the introitus, to the delivery of the last pup—these were well defined and easily observable events. This model eliminated ill-defined clinical judgments such as presence or absence of urge to bear down, which is dependent on the intensity of sacral blockade and the (human) mother's ability to co-operate.

Intense sensory and motor blockade below the lumbar region with 0.5% bupivacaine caused a prolongation of the delivery process in the rats by a factor of 3 in the absence of obstetric interference, such as forceps delivery, which might have been performed in the clinical setting. Such a prolongation of labour was almost certainly the result of the removal of Ferguson's reflex and the absence of active maternal effort in bearing down (Ferguson, 1941; Debackere, Peeters and Tuyttens, 1961; Goodfellow et al., 1983).

The high perinatal mortality observed in the group receiving spinal blockade is probably related to the prolonged "second stage of labour". Maternal and fetal acid–base measurements during human labour showed that there was a progressive fetal acidosis in mothers in the second state of labour receiving extradural analgesia, even if the mother was not pushing (Pearson and Davies, 1974). Our high rate of fetal loss was probably the end result of this deleterious effect of prolonged labour and was unlikely to have been caused by toxicity arising from systemic absorption of bupivacaine. This effect was not observed in the group receiving the same dose of local anaesthetics by the intraperitoneal route.

Maternal arterial pressure was not measured in this experiment because it was technically difficult in a mobile animal. However, it is reasonable to assume that the arterial pressure would remain reasonably stable with a continuous infusion during a mean time of 11.6 h. In addition, the animals moved around apparently normally to drink, the extent of blockade was kept steady (below the lumbar region), and aorto–caval compression does not occur in rats because of their natural semi-prone position.

The effects of slowed labour also resulted in death of two mother rats during delivery, probably because of the prolonged "second stage".

Discussion about the effects of sensory and motor blockade on the incidence of forceps delivery and, on the other hand, whether delayed maternal pushing is beneficial will continue (Studd et al., 1980; Maresh, Choong and Beard, 1983; Phillips and Thomas, 1983). We now intend to use this model to test the influence of various concentrations of other local anaesthetics and analgesics on the delivery process. Cocaine administered intraspinally, for instance, offers a selective blockade in animals (Bahar et al., 1984), and other drugs may prove to have advantages.

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IMPAIRED METABOLIC ACTIVITY OF PHAGOCYTIC CELLS AFTER ANAESTHESIA AND SURGERY

L. BARDOSI AND M. TEKERES

SUMMARY

Peripheral blood leucocytes and their phagocytosis-associated metabolic activity were studied in 65 patients after elective surgery representing similar degrees of surgical trauma. Halothane (group A) or neurolept (group B) anaesthesia were given to 50 patients. Fifteen patients had extradural blockade only (group C). Leucocytosis was observed immediately after surgery in group B: patients in groups A and C responded more slowly. The higher 2nd-day values were followed by a decrease in leucocyte numbers on the 5th day. Although patients in groups A and B showed immediate decreases in nitroblue tetrazolium reduction, recovery was noted only in group B on the 5th day after operation. It is postulated that leucocytes with damaged membranes and receptors are probably lacking in the necessary functional integrity to fight invading microorganisms.

The phagocytic response to external pathogenic challenge is prompt, with an increase in the number of phagocytes, and in their motility and bactericidal activity. General anaesthesia, when associated with surgery, is one of the factors which may suppress these functions and lead to a deterioration in host defence mechanisms and an increase in susceptibility to infection after operation (Koenig, Koenig and Stoeckel, 1978). Indeed, postoperative leucocytosis with concurrent lymphocytopenia is common. However, it seems unlikely that this increase in the number of leucocytes is linked with enhanced functional capabilities. Indeed, a decrease in phagocytic activity has been demonstrated under these circumstances by several workers, but it is not clear whether the changes resulted from the use of general anaesthetic agents or from surgical stress, the latter, perhaps, acting by releasing endogenous steroid and catecholamines (Slade et al., 1975; Bruce, 1976; Bowers, O'Flaherty and Simmon, 1977; Walton, 1978). Impaired chemotactic motility has been reported after *in vitro* exposure to nitrous oxide. The effect of halothane on this function is still controversal (Nunn et al., 1979; Nunn and Morain, 1982).

Phagocytosis represents only the first step in the elimination of foreign substances. The capability to kill the ingested micro-organisms is highly dependent on metabolic activation inside the cell. As a result of this activation there are increases in the production of hydrogen peroxide and of active superoxide (O_2^-) radicals, together with activation of the hexose monophosphate shunt and changes in the glucose metabolism of the cell membrane (Baehner and Nathan, 1968). The present study was designed to investigate the influence of general anaesthesia and surgery on the bactericidal function of peripheral blood phagocytic cells assessed by the capability to reduce nitroblue tetrazolium (NBT) dye *in vitro* before and after phagocytosis.

PATIENTS, MATERIALS AND METHODS

Samples of peripheral venous blood were obtained from 65 patients (25 females) aged 20–50 yr (mean 34 yr) undergoing elective surgery for meniscectomy, stripping of varicose veins or bilateral herniorrhaphy. Of these patients, 25 were anaesthetized with nitrous oxide, oxygen and halothane, with spontaneous ventilation (group A), and 25 with

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a neuroleptanaesthetic technique (nitrous oxide–oxygen–fentanyl–droperidol) and controlled ventilation (group B). A further 15 patients received extradural blockade only (group C). The different operations were distributed equally between the study groups. Patients on medical treatments or with evidence of infection, endocrine disease or anaemia were excluded. Twenty-five healthy volunteers from the same age group served as controls.

Anaesthetic technique

Premedication was administered i.m. 1 h before surgery and consisted of pethidine 50 mg, promethazine 25 mg and atropine 0.6 mg for groups A and C, and fentanyl 0.1 mg, atropine 0.6 mg and droperidol 5 mg for group B.

Halothane anaesthesia (group A). Anaesthesia was induced with thiopentone 3 mg kg^{-1}. Suxamethonium 1 mg kg^{-1} was administered to provide sufficient muscular relaxation to permit intubation of the trachea. Anaesthesia was maintained with 70% nitrous oxide and 1–2.5% halothane in oxygen.

Neuroleptanaesthesia (group B). Induction of anaesthesia and intubation of the trachea were as for group A. Pancuronium 0.1 mg kg^{-1} was used for the subsequent maintenance of myoneural blockade. Fentanyl 5 μg kg^{-1} and droperidol 0.2 mg kg^{-1} were given as supplements.

Extradural analgesia (group C). An extradural catheter was inserted through the L3–L4 space. After a test dose, 2% lignocaine 18 ml together with adrenaline 5 μg ml^{-1} was given with the patient lying supine. During the operation the patients received an infusion of physiological saline i.v. No blood transfusion was given. The extradural catheter was removed as soon as the surgical procedure had been completed.

Postoperative analgesia was provided (pethidine 1 mg kg^{-1}) for each group if required. No antibiotics were administered during surgery.

Laboratory investigations

Samples of peripheral venous blood (25 ml) were collected from each patient immediately after surgery, 1 day and 5 days later. Absolute and differential leucocyte counts were obtained. The leucocytes were isolated and a quantitative NBT-test performed as described by Baehner and Nathan (1968). Leucocyte viability, as assessed by trypan blue exclusion, was greater than 95%.

The NBT-test was performed on the leucocyte preparations before and after phagocytotic challenge carried out by adding latex particle suspension (Bacto-Latex 0.81 Difco, U.S.A.), 0.1 ml–0.5 ml of leucocyte preparation (25 × 10^6 cells ml^{-1}) and 1 ml of Hank's balanced salt solution (HBSS) in the presence of heat-inactivated human AB serum 0.25 ml. NBT solution (Sigma, St Louis, MO) (0.1%) 0.5 ml in phosphate buffered saline (pH 7.2) was added to the samples. After incubation at 37 °C for 15 min the blue-coloured formazane was extracted with pyridine in a hot-water bath and measured by photometry at 515 nm wave length using a Spectromom 195 spectrophotometer (MOM, Hungary). To control the engulfment of latex particles a sample (0.1 ml) was removed from the preparation before pyridine extraction, smeared, and stained with Wright's stain. The slides were then examined by light microscopy.

TABLE I. *White blood cell counts and lymphocyte counts with the results of the nitroblue tetrazolium test both with and without stimulation with latex. Mean values* ± SD

	Control ($n = 25$)	Days	A Halothane ($n = 25$	B Neurolept ($n = 25$)	C Extradural ($n = 15$)
WBC count (cell μlitre^{-1})	4696±1137	1	4548±1544	5736±1877	4680±1388
		2	5808±1592	6982±2779	5553±1709
		5	4018±810	4858±1577	4546±1114
Lymphocyte count (cell μlitre^{-1})	1541±590	1	1388±428	1406±767	1444±561
		2	1192±401	1324±403	1375±550
		5	1022±232	1461±485	1330±476
NBT reduction unstimulated (optical density)	0.3082±0.0893	1	0.2972±0.0725	0.2278±0.0635	0.3073±0.0808
		2	0.2970±0.0912	0.2814±0.0853	0.2443±0.0652
		5	0 2370±0.0637	0.3044±0.0780	0.3176±0.0942
NBT reduction latex-stimulated (optical density)	0.4638±0.0578	1	0.3435±0.0878	0.2872±0.0980	0.3816±0.1066
		2	0.3634±0.1087	0.3444±0.1200	0.3060±0.0820
		5	0.2840±0.0817	0.3764±0.1224	0.4053±0.1165

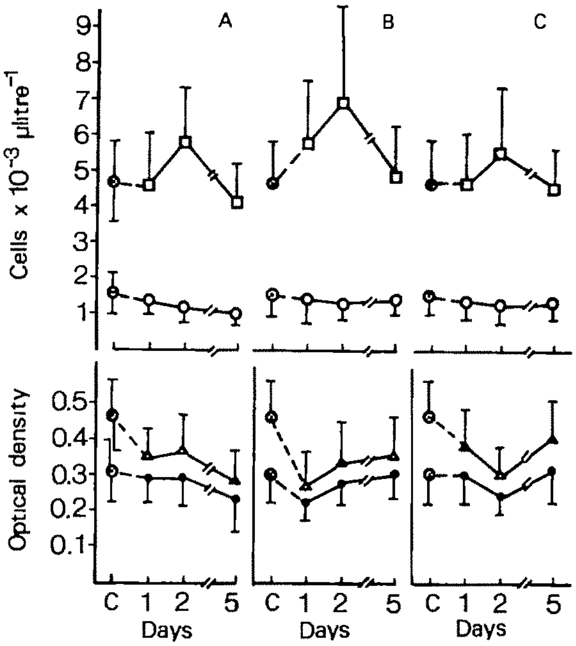

FIG. 1. Pre-(●) and post-(△) phagocytotic reduction of nitroblue tetrazolium by leucocytes (lower curves), and changes in the white blood cell (□) and absolute lymphocyte (○) count (upper curves) after anaesthesia and surgery. A: halothane group; B: neurolept group, C: extradural group. ⊖ = Controls.

Statistical analysis

Paired Student's *t* test was used for evaluation of the significance of changes over time in the study groups before and after latex stimulation and the unpaired *t* test to analyse the differences between the groups, based on their deviation from the control values.

RESULTS

The results are summarized in figure 1 and shown in detail in table I.

Effect of anaesthesia and surgery on the absolute and differential blood leucocyte count

Leucocyte count. On the first day after operation, significant leucocytosis was observed in group B ($P < 0.05$), no increases in leucocyte count being noted in groups A and C. However, by the 2nd day after operation, there was a leucocytosis in all three groups. The increases were significant in groups A and B ($P < 0.05$), but did not achieve significance in group C when compared with control values. By the 5th day, leucocyte values had declined significantly from the values obtained on the 2nd day ($P < 0.05$) in each group. In group A the leucocyte count had decreased to below the control value ($P < 0.05$).

Lymphocyte count. Close inspection of the upper lines on figure 1 suggests that there was a lymphopenia after surgery and anaesthesia in all groups: statistical evaluation demonstrated this to be significant ($P < 0.05$) in groups A and B on day 2, and in group A on day 5. No statistically significant change was noted in group C.

Changes in the phagocytosis-associated metabolic stimulation of leucocytes after anaesthesia and surgery

Figure 1 suggests that there was an increase in metabolic activity of phagocytes after latex stimulation, but that this metabolic stimulation was less marked after anaesthesia and surgery than it had been before. In fact, the difference between the activity before and after stimulation by latex was significant both before, and on each of the days studied after, anaesthesia ($P < 0.05$ in every case and in every group except for the 1st and 5th days in group A and the 2nd day in group B). In addition, there was a decrease in the activity before latex stimulation in group A which was significant on the 5th day, in group B on the 1st day, and in group C on the 2nd day only. After latex stimulation, however, the situation was different. In groups A and B the level of activity was below the control values on each of the days studied, but in group C the difference was significant on the 1st and 2nd days only.

DISCUSSION

Surgical trauma, steroid and catecholamine mobilization, neural impulses from damaged tissues, blood loss and anaesthetic agents are likely to contribute to the development of immunosuppression after operation. On the other hand, extradural analgesia is claimed to prevent postoperative lymphocytopenia and substantially decrease granulocytosis (Newsome and Rose, 1971; Cullen and Van Belle, 1975; Kehlet, 1978; Rem, Brandt and Kehlet, 1980).

The functions of phagocytic cells have been the subject of extensive investigation. In the current study those patients who were given neuroleptanaesthesia had an immediate leucocytosis, while in the halothane and extradural groups this reaction was delayed.

Nunn and Morain (1982) suggested that nitrous oxide might be responsible for the decrease in the motility of human neutrophils *in vitro*. As nitrous oxide was used in groups A and B, the administration of halothane in group A might provide an explanation for the difference between the leucocyte responses. Possibly, halothane, either alone or in combination with nitrous oxide, opposes the normal leucocyte response to tissue damage, causing a delay in the onset of granulocytosis after operation. In the current study, as soon as the effect of the local anaesthetic had worn off, an increase in the leucocyte count occurred in the extradural group also. A shift towards normal values was detected by the 5th day after operation in each group; indeed, in group A the number of leucocytes decreased well below the control values (fig. 1A). This phenomenon is not easy to explain in the light of current knowledge.

In our study, metabolic activity, as related to bacterial killing, appeared to be affected by anaesthesia and surgery. Although there was an immediate decrease in NBT-reducing activity in patients in groups A and B, the tendency for recovery was noted only in group B patients, to whom nitrous oxide was given as the sole inhalation anaesthetic agent. The unstimulated values in this group reached the control value on the 5th day after operation.

Sympathetic blockade and the lack of inhalation anaesthetic agents could explain why phagocytes derived from group C patients were not affected immediately by surgery and maintained their normal unstimulated NBT-reducing capacity. Values after latex stimulation suggested, however, that phagocyte function had not remained totally unaffected. Depression of metabolic activity developed on the 2nd day, appearing to indicate the end of the protective effect of afferent blockade and the build up of a "stress-associated" response.

The influence of anaesthetic agents can be either synergistic or antagonistic with surgical stimuli in modifying "phagocytosis-related" metabolic changes. Their effect is presumably related to physico-chemical, pharmaco-physiological and pharmacokinetic properties. Halothane has been shown to inhibit oxygen consumption in tissue cultures and to block electron transfer between NADH and flavoproteins, which are essential in the production of bactericidal H_2O_2 (Fink and Kenny, 1968; Besombe and Longimur, 1971). Inhalation anaesthetics with high lipid solubility are liable to cause alterations in the cell membrane and, thus, impede the transmembrane cytoskeletal control of bacterial recognition, ingestion and metabolic activation, leaving behind a handicapped leucocyte population. The damaged cells or their replacements from the bone marrow, itself affected by the anaesthetics used, probably do not possess the functional integrity which enables them to develop a reaction to bacterial invasion.

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PHOTO-ELECTRIC PLETHYSMOGRAPHY AS A MONITORING DEVICE IN ANAESTHESIA

Application and Interpretation

J. C. DORLAS AND J. A. NIJBOER

SUMMARY

The optical principle of photo-electric plethysmography is described and the clinical significance of changes in the amplitude of the plethysmogram discussed. Physiologically, changes in blood volume pulsations depend on the distensibility of the vessel wall as well as on the intravascular pulse pressure. The importance of both factors in the interpretation of changes in the arterial pulse amplitude is illustrated by examples from 500 continuous recordings. In addition, it is shown that changes in the height of ventilatory waves may be of diagnostic significance.

Photo-electric plethysmography can be used during anaesthesia to monitor the pulsations associated with changes in blood volume in a peripheral vascular bed, and may be useful as a detector of imminent haemodynamic disturbance (Foster, Neumann and Rovenstein, 1945; Dorlas and Zeelenberg, 1970; Otteni, Sauvage and Gauthier-Lafaye, 1970). When displayed continuously on an oscilloscope, the plethysmograph indicates electro–mechanical dissociation (Kleine, Dorlas and Moesker, 1972) and arrhythmias clearly (Sara and Shanks, 1978). Furthermore, it can detect the responses of the autonomic nervous system to stressful stimuli (Kumazawa, Kobayashi and Takagi, 1964; Johnstone, 1967), and the effects of anaesthetic drugs (Dorlas, Bartstra and Zeelenberg, 1969; Körner, 1974). It may be used as an adjunct in the Allen's test (Allen, 1929; Brodsky, 1975). The device is non-invasive, and can be applied easily and rapidly.

However, despite these advantages, the method is not applied universally. This may be because of unfamiliarity with the method as well as doubts about its validity. Thus, we review some fundamental aspects and our own experience from 500 continuous recordings in this article (in a following paper the differences between finger and ear plethysmography will be discussed).

PHOTO-ELECTRIC PRINCIPLE

The basic principle behind the method, first reported by Hertzman (1938), is relatively simple. A small light source and a photo-sensitive detector (photo-electric cell) are attached to an appropriate part of the skin (fig. 1). The emitted light is scattered and partly absorbed in the tissues. Another part of the light emerges again through the skin and is detected by the photo-electric cell. The latter can be positioned either beside, or opposite, the light source, resulting in the reflection or transmission method, respectively. The intensity of the light detected by the photo-cell is determined by the opti-

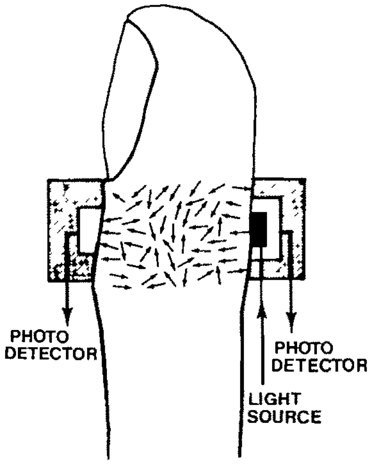

FIG. 1. Application of photo-electric transducer to the finger in the reflection and transmission modes.

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cal density of the solid tissues such as skin, connective tissue and bone, and by that of the varying amount of blood in the vascular bed (Weinman and Manoach, 1962). Blood has a light absorption coefficient which is higher than that of the surrounding tissues (Kramer et al., 1951; Zijlstra and Mook, 1962), so that increases in the amount of blood give rise to a decrease in the total amount of light detected (Challoner and Ramsey, 1974; Challoner, 1979). On the other hand, the erythrocytes (Jansonius, 1959) and the vessel walls (Weinman, Hayat and Raviv, 1977) also reflect some light and, when blood flow is pulsatile, this reflection will increase simultaneously with the pulsations because of the orientation effect of the erythrocytes (Visser et al., 1976), and the movement of the vessel walls. Normally, however, the effect of absorption predominates (Nijboer, Dorlas and Mahieu, 1981), so that arterial pulsations will produce small reductions in the light detected, synchronously with the heart beat. These variations are only small and proportional (1–2%) to the total amount of light detected. Only the variations in detected light are amplified and converted to a voltage signal which can be displayed continously, and recorded as a plethysmogram. In most plethysmographs a decrease in light is recorded as an upward deflection in the plethysmogram. For the recordings reviewed in this article, the Philips peripheral pulse module (type XV 1504/00) (Now: Honeywell Medical Electronics, Best, The Netherlands) was used. Its transducer consists of a diode emitting near infrared light and a matching photo diode for detection.

Since the signal is also electronically chopped, the transducer is relatively insensitive to ambient light and does not produce heat. The transducer is attached to a finger or ear where pulsations in the cutaneous vascular bed are measured almost exclusively (Hertzman, 1938).

ORIGIN AND MEANING OF THE PLETHYSMOGRAPHIC WAVES

Figure 2B shows the photo-electric finger plethysmogram of an anaesthetized patient, recorded at two different paper speeds. Two wave forms can be distinguished. The rapid excursions are synchronous with the heart beat. They arise because volume distensions of the root of the aorta are propagated along the walls of the vascular tree to the terminal arterial bed from which the plethysmogram is recorded. The slower waves are caused by ventilation-dependent changes in intrathoracic pressure, which are transmitted to the periphery (Foster, Neumann and Rovenstein, 1945; Otteni, Sauvage and Gauthier-Lafaye, 1970; Sara and Shanks, 1978). These pressure changes produce variations in blood volume which arise principally in the venous bed, since the venous compliance is 10 times greater than the arterial (Wilkins and Bradley, 1946). These "ventilatory waves" (a more appropriate description than respiratory waves), become especially prominent during artificial ventilation or airway obstruction. The arterial pulse wave is generally used for monitoring purposes (Elings, 1959) because its amplitude indicates the arterial blood pulsations reaching the periphery. However, during anaesthesia, and especially when recorded with a low paper speed, the amplitude of the arterial pulsations is sometimes difficult to distinguish from the ventilatory waves upon which the arterial pulsations are superimposed. This influence of the ventilatory waves may be decreased by the elevation of the measuring site above heart level, so that the venous system will collapse and the changes in intrathoracic pressure are no longer transmitted. However, during anaesthesia this manoeuvre may not suffice. Therefore, a new kind of peak detector has been developed (Sluiter et al., 1981) which calculates the

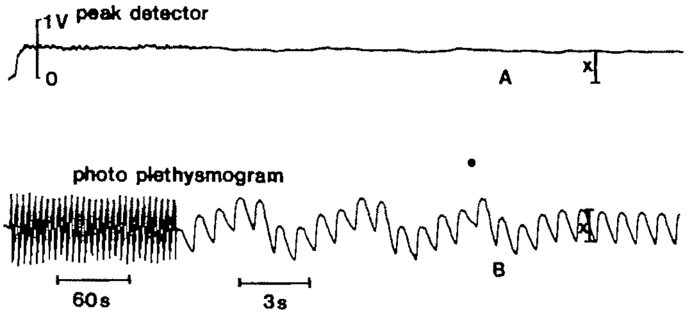

FIG 2. Photo-electric finger plethysmogram recorded with two paper speeds. A· Arterial pulse amplitude calculated by a peak detector which is not influenced by ventilatory waves. B· Rapid arterial waves and slower ventilatory waves. At the right side the ventilation is stopped temporarily.

peak-to-peak amplitude of each arterial pulse wave and eliminates the slower ventilatory component (fig. 2A). In this paper the peak detector signal is shown only when the exact course of the arterial pulse amplitude is accentuated.

For the interpretation of the photo-electric plethysmogram, it should be realized that changes in light are measured which are proportional to the total amount of light detected and which cannot be calibrated (Nijboer, Dorlas and Mahieu, 1981). Therefore, the amplitude of the photo-electric plethysmogram does not indicate the height of the arterial pulse waves in a quantitative way. All the same, several authors (Elings, 1959; Hertzman, 1959; Zijlstra and Mook, 1962) have reported a good correlation between finger photo-plethysmographic amplitude and the blood flow in the finger.

We have also compared photo-electric plethysmography with mercury-in-rubber strain-gauge plethysmography, the latter being applied in the a.c. mode, without applying venous occlusion, so that only the arterial blood volume pulsations were measured. The plethysmograms were recorded simultaneously from adjacent fingers during anaesthesia (fig. 3). The changes in amplitude of both plethysmograms proved to be identical in 98% of the total number of changes recorded in 104 patients (Nijboer, Dorlas and Prins, 1983). This means that changes in the amplitude of the photo-electric plethysmogram, just like the blood volume pulsations (ΔV), depend on the distensibility of the vascular wall (D) as well as on the intravascular pulse pressure (ΔP). This relationship was given by Burton (1972) as $\Delta V = D.\Delta P$.

In the peripheral arterial bed, the distensibility factor depends mainly upon the tone of vascular smooth muscle, which is controlled by the autonomic nervous system. As a result of the special mechanical arrangement of vascular smooth muscle fibres (Burton, 1954), the effect of autonomic impulses upon distensibility will be so strong that it completely predominates over the effect of pulse pressure in several regions of the body.

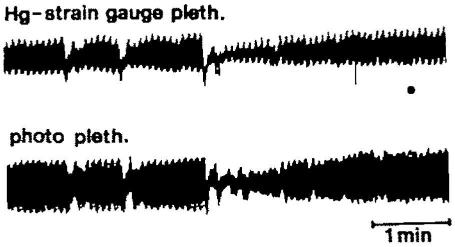

FIG. 3. Vasoconstriction during surgery recorded simultaneously from a finger with photo-electric plethysmography and mercury-in-rubber strain gauge plethysmography.

PHYSIOLOGICAL EFFECTS AND INTERPRETATION

Burch, Cohn and Neumann (1942) reported several kinds of autonomic fluctuation arising rhythmically but apparently spontaneously in the plethysmogram of conscious volunteers. Although some investigators considered that there was a connection with central temperature regulating mechanisms (Blair, Glover and Roddie, 1959; Burton and Taylor, 1940), there is still some controversy about their origin. From the autonomic fluctuations and the simultaneously recorded peak detector signal (fig. 4), we conclude that the variations in amplitude in the arterial pulse wave are small. Therefore, the autonomic fluctuations must be the result of changes in the total amount of detected light, which are predominantly determined by volume changes in the venous bed. Since the cutaneous veins are sympathetically innervated (Hertzman, 1959; Shepherd and Vanhoutte, 1975) and play an important part in the regulation of body temperature (Goetz, 1950), an association with this temperature mechanism seems plausible. The autonomic fluctuations always disappear, as Wilson (1936) observed in dogs and rabbits, on the induction of anaesthesia (Burton and Taylor, 1939; Nijboer and Dorlas, 1985). Throughout anaesthesia, on the other hand, shorter or longer-lasting periods of diminished arterial pulse wave amplitude were often noticed in the finger plethysmogram (fig. 5). The decreases in amplitude were connected with pain and stressful stimuli, but

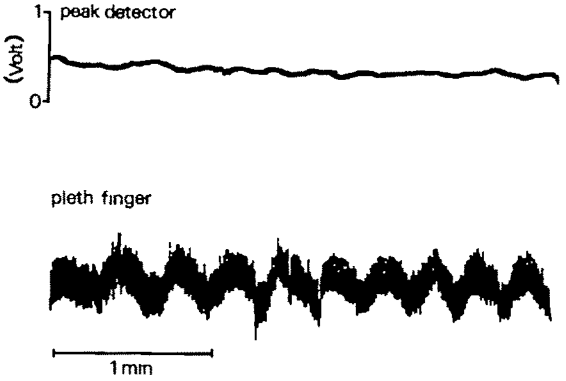

FIG 4. A Autonomic fluctuations in the finger plethysmogram of an awake patient. B· Peak detector signal showing that the variations in the amplitude of the arterial pulsations do not reflect the strong fluctuations in the plethysmogram.

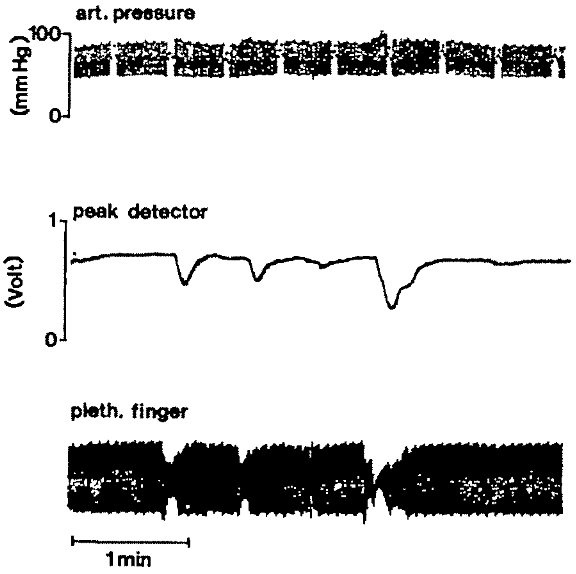

FIG. 5. Vasoconstriction in the finger plethysmogram during surgery which is not accompanied by concomitant decreases in the simultaneously recorded arterial pressure.

were not accompanied by a decrease in pulse pressure (ΔP). Therefore they have to be attributed to a decrease in distensibility (D)—that is, vasoconstriction induced by sympathetic stimulation of the smooth muscle of the peripheral arterial bed. These changes in pulse wave amplitude cannot be the result of changes in carbon dioxide concentration, because the capnogram was maintained steady in all our studies. Peripheral vasoconstriction was recorded during several periods of surgery, but we have established that there is variation between different regions of the body, for instance between finger and pinna, as will be reported in the following paper.

In the course of an anaesthetic, a gradual but pronounced decrease of the amplitude of the finger plethysmogram is often found. There is a widespread belief that this vasoconstriction is the result of cooling of the skin when exposed to the comparatively cool surrounding temperature in the operating theatre (Otteni, Sauvage and Gauthier-Lafaye, 1971). However, in studying 40 patients in whom skin temperature was measured during anaesthesia, we have found (fig. 6) that the decrease in amplitude always preceded the decrease in finger temperature (Dorlas, 1974; Nijboer, Dorlas and Prins, 1983). Therefore, the decrease in finger temperature is the result of and not the reason for, the vasoconstriction.

In vascular beds which are known to react markedly to stimuli, the responses can be inhibited by certain anaesthetic techniques or sympatholytic agents. Since, in these cases, the walls of the arterial blood vessels are more distensible, the amplitude of the plethysmogram will remain or become relatively large as a sign of vasodilatation and the amplitude will respond mainly to changes in pulse pressure. This is generally noted under neurolept anaesthesia (Buhr and Henschel, 1966), "stress-free" anaesthesia (Savege, 1978) and a high concentration of halothane (Beddard, 1965; Johnstone, 1956). Sporadically, there has been recorded during surgery a sudden increase in amplitude of the finger or ear plethysmogram, or both, which was so large that it could hardly be explained by neurogenic vasodilatation, and other causes such as an increase in pulse pressure or carbon dioxide concentration could be excluded (fig. 7). This phenomenon most often subsided in 5–10 min, and we believe that it has a humoral origin, elicited by release of some vasoactive agent.

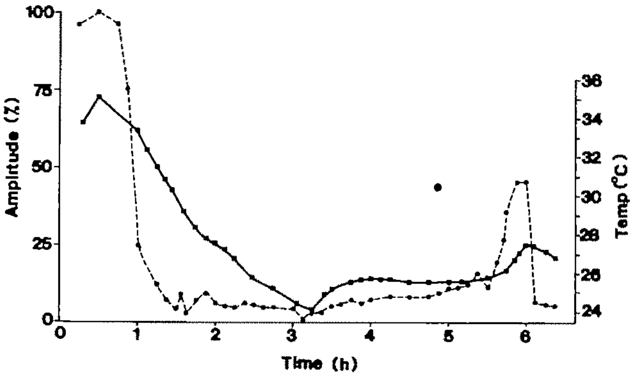

FIG 6. Illustration of the changes in plethysmographic amplitude (●—●) preceding the changes in skin temperature (■——■) when recorded simultaneously from a finger during surgery.

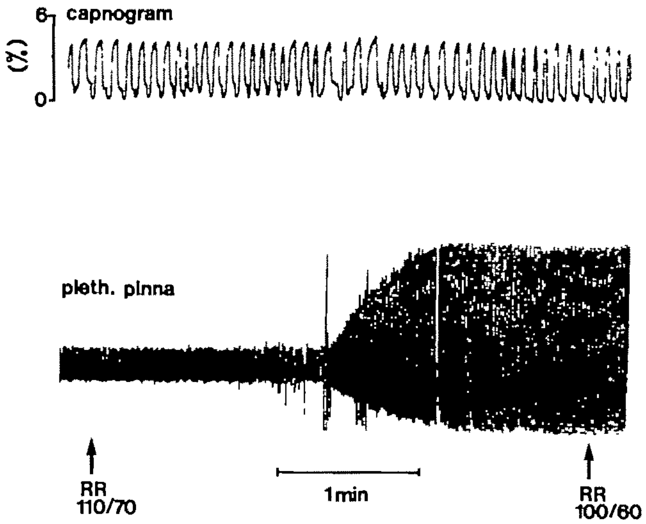

FIG. 7. Sudden, large increase in plethysmographic amplitude in a spontaneously breathing patient during surgery under general anaesthesia. The continuously recorded capnogram and the intermittently measured arterial pressure remain virtually unchanged.

EFFECTS OF THE OPTICAL PRINCIPLE

In addition to the physiological effects, factors which are connected with the optical principle of the method may influence the interpretation of the plethysmogram. Since the amplitude of the arterial pulsations is proportional to the total amount of light detected, it will also depend on the optical density of the tissues surrounding the arterial vasculature. The latter may be influenced by the pressure exerted on the skin by the transducer (Nieveen, v.d. Slikke and Reichert, 1956). De Pater, van den Berg and Bueno (1962) showed that the amplitude increased when the application pressure was increased, and that the amplitude reached its maximum at an application pressure of about 40 mm Hg. Johnstone (1976) suggested that the transducer be replaced every 20 min, because the local pressure on the finger vessels would, in his opinion, result in a gradual decrease in amplitude. This view conflicts with our own that, during the course of an anaesthetic, the amplitude of the finger plethysmogram often varies in an irregular pattern and may even increase. Moreover, these changes in amplitude correlate well with simultaneously-recorded changes in pulse wave amplitude of the mercury-in-rubber strain-gauge which, in our studies, exerted hardly any pressure on the skin of the finger tip. Therefore, we feel that the transducer should not be replaced during one continuous measurement, unless it is realized that a new situation is created in another part of the vascular bed, or by a change in application pressure.

The total amount of light detected by the photocell may also be altered by venous engorgement. Figure 8 shows that the amplitude of the continuously-recorded ear plethysmogram decreases abruptly when the patient is put in the Trendelenburg position and *vice versa*. Since no changes were noticed in the other variables, we have attributed these effects to the changes in the amount of venous blood affecting the optical density of the surrounding tissues and not to a change in the actual arterial pulsations.

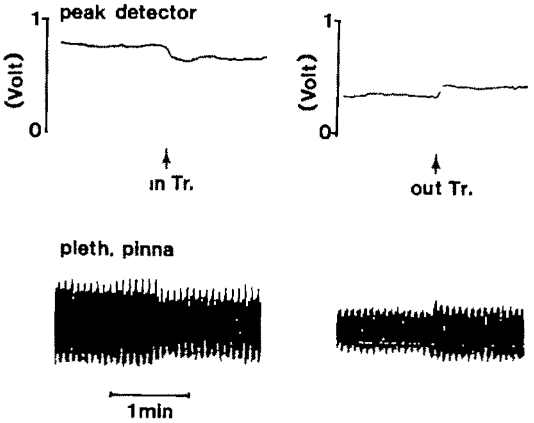

FIG. 8. "Artificial" changes in arterial pulse amplitude when a patient is placed in the Trendelenburg position (in Tr.), and another patient is replaced in the horizontal position (out Tr.).

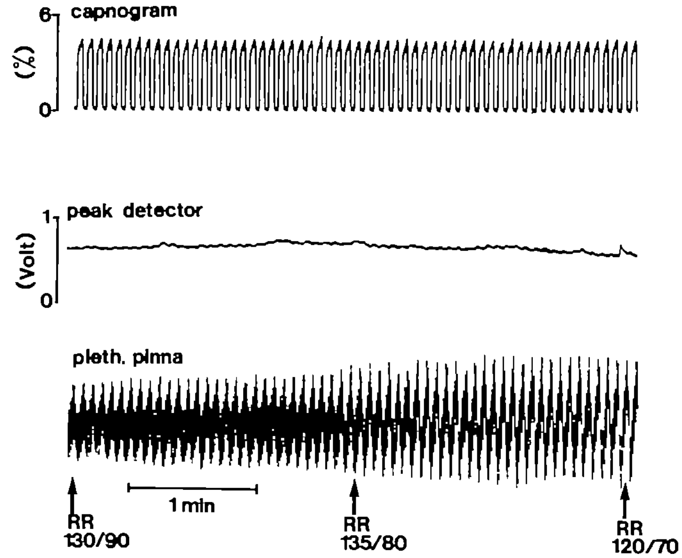

FIG. 9. Increase in height of the ventilatory waves as a result of the development of hypovolaemia, independent of eventual changes in arterial pulse amplitude, capnogram or arterial pressure.

Venous engorgement in combination with application pressure may even give rise to an inverted waveform in the reflection plethysmogram (Nijboer and Dorlas, 1982). This may happen, for instance, during arterial pressure measurement at the same arm, if the cuff is slowly deflated.

VENTILATORY WAVES

Changes in the ventilatory waves may have diagnostic significance. Their height depends mainly on the relationship between central venous pressure and the variations in intrathoracic pressure caused by ventilation, but to what degree these pressure variations are reflected in the plethysmogram also depends on the distensibility of the venous walls. The latter depends substantially on the degree of stretch caused by local venous pressure. Since this pressure decreases in association with hypovolaemia, the distensibility of the walls will increase and the height of the ventilatory waves will increase despite unchanged ventilation pressures. This may happen independently from eventual changes in arterial pulse amplitude or expiratory carbon dioxide concentration (fig. 9). On account of these considerations, an increase in ventilatory waves arising during an anaesthetic with unchanged ventilation pressures is interpreted in our department as a sign of (relative) hypovolaemia.

In conclusion, photo-electric plethysmography is a simple monitoring technique which demonstrates arterial blood volume pulsations, generally superimposed on slower ventilatory waves. Changes in the arterial pulse amplitude during anaesthesia depend mainly on neurogenic or humorally-determined changes in distensibility of the arterial walls, and sometimes on changes in pulse pressure. An increase in the height of the ventilatory waves may be a sign of (relative) hypovolaemia. For the assessment of changes in the plethysmogram, the transducer should not be replaced during one continuous recording. From the optical point of view, the application pressure and the degree of venous engorgement are of importance.

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COMPARISON OF PLETHYSMOGRAMS TAKEN FROM FINGER AND PINNA DURING ANAESTHESIA

J. A. NIJBOER AND J. C. DORLAS

In the preceding paper it was noted that photo-electric plethysmography could be used to monitor several aspects of the circulation (Dorlas and Nijboer, 1985). During anaesthesia the plethysmogram is obtained either from the cutaneous vascular bed of the digits, where the reflection method is used, or from the ear, where the transmission method is the obvious choice. However, when reviewing data from 500 patients in whom plethysmograms were recorded simultaneously from finger and ear during anaesthesia, we observed a marked difference in the responses to various stimuli.

In the first instance, one might be inclined to ascribe the differences to the use of the reflection and transmission methods, respectively. However, this possibility was excluded by a previous study which demonstrated no difference in the light/voltage relationship, when applied to the finger or ear (Nijboer, Dorlas and Mahieu, 1981). Therefore, the difference in response must result from factors which control the size of the blood volume pulses (ΔV) in finger and pinna, these being the variations in intravascular pressure (ΔP) and the distensibility (D) of the vascular walls. The relationship is given by Burton (1972) as $\Delta V = \Delta P.D$.

The peripheral pulse pressure in this formula is derived from the pressure in the root of the aorta, so that it can hardly account for the difference in response between fingers and ear. Consequently, we believe that the difference in response has to be attributed mainly to a difference in distensibility of the vascular walls. Since the distensibility of the arterial vascular bed depends chiefly on the tone of vascular smooth muscle, it will be controlled primarily by the autonomic nervous system (Burton, 1954).

SUMMARY

Pulse plethysmograms from finger and pinna were recorded simultaneously during anaesthesia, and marked differences in their response to various stimuli recorded. The differences have been illustrated by a number of examples.

RESPONSES IN FINGER PLETHYSMOGRAM

Figure 1 depicts plethysmograms (Honeywell Philips peripheral pulse module, described in the accompanying article (Dorlas and Nijboer, 1985)) from finger and pinna recorded simultaneously at the beginning of an anaesthetic.

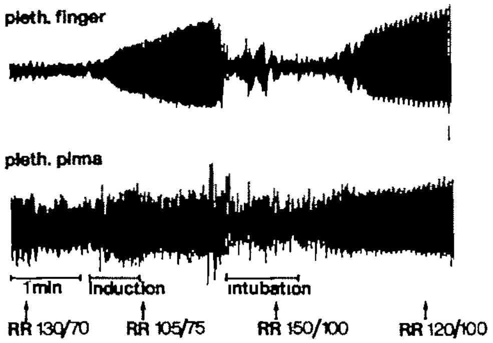

FIG. 1. Photo-electric plethysmograms recorded simultaneously from finger and pinna, showing the difference in response at the induction of anaesthesia.

On induction the most striking phenomenon was the marked increase in amplitude which occurred in the finger plethysmogram and which did not occur in the ear plethysmogram. This increase in "finger" amplitude (temporarily interrupted by intubation) has been recorded in 95% of inductions, and is independent of the induction agent used. This effect was

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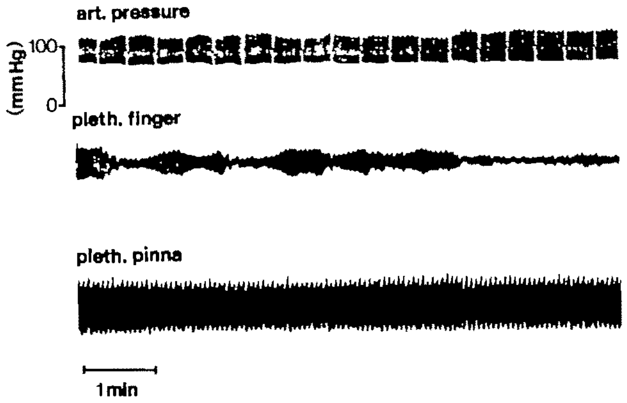

FIG 2. Stressful surgical stimuli: differences in response between the photo-electric plethysmogram from finger and pinna, and the arterial pressure.

also reported by Strandness and colleagues (1964), Otteni, Sauvage and Gauthier-Lafaye (1970), and Johnstone (1974a). Because pulse pressure does not increase, the increase in finger amplitude is attributed to a decrease in vascular smooth muscle tone,—that is, vasodilatation. Since this vasodilatation is found particularly in the finger, where the walls of the cutaneous vessels are innervated by α-adrenoceptors (Goodman and Gillman, 1965), there must be a loss of sympathetic tone induced centrally by the suppression of psychic stimuli. Therefore, it is called an "induction sympatholysis".

Intubation, on the other hand, produced a profound decrease in amplitude, which was also observed principally in the finger plethysmogram. Since this decrease in amplitude was not accompanied by a decrease in pulse pressure, it had to be caused by constriction of vascular smooth muscle. This vasoconstriction shows that, although the patient was anaesthetized, the reactivity of the finger vessels to stressful stimuli was preserved, and predominated over the effect of pulse pressure. Furthermore, it may be noted that, initially, the plethysmograms showed small rhythmic and apparently spontaneous fluctuations: these are characteristic of the awake state (Burch, Cohn and Neumann, 1942) and always disappear during the induction of anaesthesia (Dorlas and Nijboer, 1985). Following intubation of the trachea, ventilatory waves became prominent, as a result of the increase in variations in intrathoracic pressure during artificial ventilation (Sara and Shanks, 1978).

Throughout surgery vasoconstriction—of shorter or longer duration—was evident in the finger in around 75% of our recordings. This was always accompanied by a small increase in systolic arterial pressure. The ear plethysmogram remained stable (fig. 2). These reactions are usually caused by adrenergic responses to stressful stimuli (Goddard, 1982). However, more prolonged vasoconstriction in the finger vascular bed may be part of a general compensation mechanism to an imminent disturbance of the circulation (Dorlas, 1974).

Towards the end of surgery a gradual decrease in amplitude occurred in the finger plethysmogram only (in 80% of our recordings) (fig. 3). This may be attributed to an increase in sympathetic tone during a lighter plane of anaesthesia.

From these observations it is evident that changes in amplitude in the responsive finger plethysmograms are determined by variations in distensibility of the cutaneous vessels under the influence of sympathetic stimuli. However, the reactivity of the vascular bed in the finger can be inhibited by several

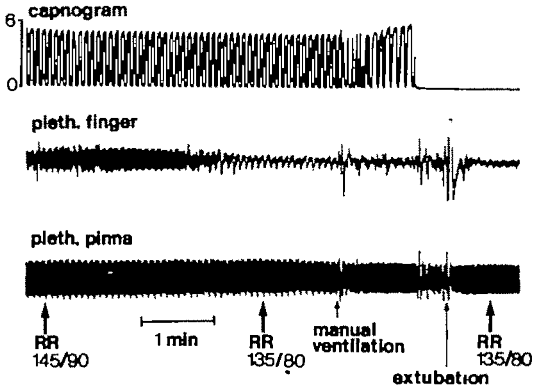

FIG. 3 Example of the plethysmographic pattern in the period of awakening from anaesthesia.

anaesthetic agents, as is shown for dehydrobenzperidol in figure 4. Similar effects have been seen with halothane, fentanyl and pethidine (Beddard, 1956; Otteni, Sauvage and Gauthier-Lafaye, 1970; Johnstone, 1974a). The blocking effect of these agents is dose-dependent and varies from patient to patient. Therefore, we feel that the amplitude pattern of the finger plethysmogram may also be used to monitor the effect of "stress-free" anaesthesia. If the blockade is effective, the influence of changes in wall distensibility is eliminated and the amplitude of the plethysmogram will respond to changes in pulse pressure only (Beddard, 1965).

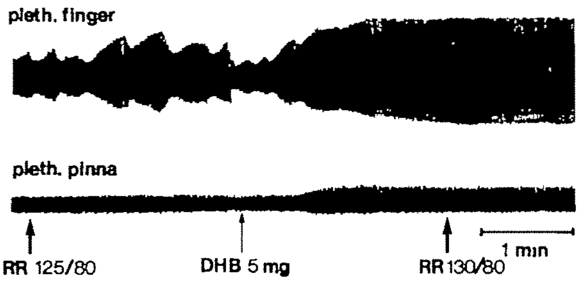

FIG 4 Effect of dehydrobenzperidol (DHB) on the reactivity of the finger plethysmogram.

RESPONSES IN EAR PLETHYSMOGRAM

Plethysmograms taken from the pinna were similar to those recorded from the blocked vascular bed in the finger since, in the ear, vasoconstrictor responses are much less pronounced, and only occurred in about 5% of our records. Therefore, the amplitude of the ear plethysmogram will respond mainly to changes in pulse pressure. Figure 5 shows a gradual decrease in amplitude, accompanied by a decrease in systolic arterial pressure, whereas amplitude in the finger and the expired carbon dioxide concentration remained stable. Sometimes, this occurs directly after the beginning of laparotomy and the insertion of the intra-abdominal packs. Since these may interfere with venous return and decrease stroke volume, it suggests a relationship between amplitude in the ear plethysmogram and pulse pressure (Beddard, 1965). However, in a retrospective study of 100 recordings, a significant correlation between amplitude in the ear plethysmogram and pulse pressure could not be substantiated (unpublished observations).

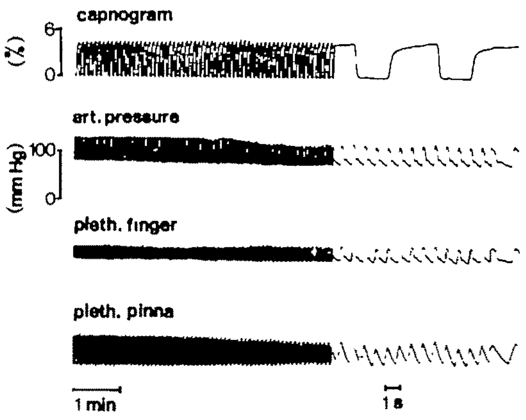

FIG. 5. Decrease in amplitude of the ear plethysmogram in comparison with other variables at the onset of intra-abdominal manipulations.

The other factor which determines the plethysmographic amplitude is the distensibility of the vascular walls, but it has been shown already in this article that the vascular smooth muscles in the ear respond minimally to stressful stimuli. Therefore, the distensibility of the vasculature of the ear has to be controlled by mediators other than those in the finger. A difference in control was reported by Johnstone (1974b), who compared the plethysmogram taken from fingers, nose and cheek. Burton (1961) mentioned that there was little evidence of reflex vasomotor control in the skin of head and upper thorax. This "blush area," however, in contrast to the cutaneous blood vessels of the extremities, demonstrated a predominance of control by circulating pressor agents. Such a control mechanism would agree with the sudden and marked increase in "ear" amplitude we have observed during the final stages of anaesthesia in 42 of 100 patients in whom pethidine was the main analgesic (fig. 6).

The increase in amplitude in the ear plethysmogram occurred spontaneously or after a mechanical stimulus, but without a corresponding further increase in pulse pressure, and there was no correlation with end-expired carbon dioxide concentration. On the other hand, it did seem to be connected with awakening from anaesthesia, and with the drugs used during anaesthesia. Therefore, it is tempting to suggest a relationship with the release of vasoactive agents like catecholamines or central neurotransmitters. These might induce a marked increase in vascular distensibility which only occurs in the ear.

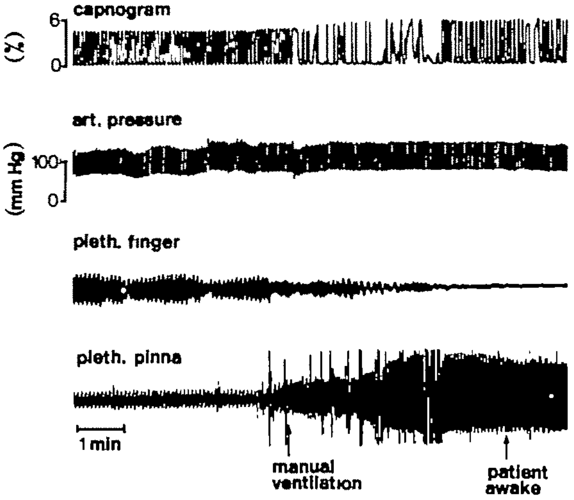

FIG. 6. Example of a sudden and marked increase in ear amplitude in comparison with other variables as the patient regains consciousness.

In conclusion it may be said that changes in the amplitude of the finger plethysmogram may be interpreted as the responses of the peripheral vascular bed to sympathetic stimuli. If this reactivity is blocked, the amplitude of the finger plethysmogram will reflect only changes in pulse pressure. The ear plethysmogram responds minimally to stressful stimuli. It is, therefore, more suitable as a monitor of the systemic circulation and, perhaps, even of stroke volume, but interpretation of changes in amplitude may be influenced by circulating vasoactive substances.

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INJURY TO TERMINAL BRANCHES OF THE TRIGEMINAL NERVE FOLLOWING TRACHEAL INTUBATION

N. S. FAITHFULL

SUMMARY

Injury to multiple terminal branches of the maxillary and mandibular divisions of the trigeminal nerve is described. The injury occurred following difficult tracheal intubation using a retrograde technique. The possible anatomical basis of the injury is described.

Although tracheal intubation is one of the commonest manipulations undertaken by the anaesthetist, complications are few in number and are generally limited to sore throat, and minor contusions or lacerations of the oropharanyx. An unusual case of injury to a number of the terminal branches of the 5th cranial nerve is reported.

CASE REPORT

In a 33-year-old patient about to undergo Caeserean section for delivery of her second child, preoperative examination revealed no abnormalities of note, and biochemical and haematological investigations were within their normal ranges. Although somewhat obese, the patient did not appear to have any anatomical abnormalities that would suggest that intubation of the trachea might be difficult.

No premedication was administered and anaesthesia was induced with thiopentone 200 mg i.v. Suxamethonium 50 mg was given. On laryngoscopy no laryngeal structures were visible and considerable effort was required to visualize the tip of the epiglottis. Intubation of the trachea, and attempts to bring the laryngeal opening into a suitable position by cricoid manipulation, were unsuccessful. Following atropine 0.5 mg, the patient received suxamethonium 25 mg repeatedly to maintain muscular paralysis and the lungs were ventilated with 67% nitrous oxide in oxygen. Further attempts to pass the tracheal tube (Portex 8 mm) using a variety of guide wires were unsuccessful and it was decided to proceed using a retrograde approach (Faithfull, 1982). An extradural needle was passed percutaneously through the cricothyroid membrane into the trachea and an extradural catheter placed in the pharynx. Once this catheter had been attached to a suction catheter, the latter was drawn down between the vocal cords by traction on the part of the extradural catheter extending from the skin in the neck. Initially, attempts at intubation by passing an 8-mm armoured latex tube over the suction catheter were unsuccessful. However, eventually, successful placement of the tracheal tube was achieved through the left nostril—using the same retrograde technique. At the end of the operation the tube was removed after the patient had recovered full consciousness.

Two hours after surgery, the patient complained of numbness of the tip of her tongue and of the mucosa of the left lower and upper lips. The numbness was confined to the medial half of the lips and on no occasion was there confluence of sensory loss around the corner of the mouth. It was thought that these effects were caused by the lignocaine spray that had been used before intubation. However, the symptoms were still present next day, and on examination, there was a decrease in sensation to pinprick over the areas indicated in figure 1. The primary area of sensory loss was centred on the tip of the tongue over a radius of about 1 cm. In addition, further loss of sensation was found in an area of skin of the upper lip which extended from the mid-line along the mucocutaneous junction, for a length of about 1.5 cm. This area extended either side of the mucocutaneous junction for about 0.5 cm. A similar

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but slightly larger area of loss of sensation to pinprick was found on the left lower lip. There was no loss of taste sensation and secretomotor activity was not obviously impaired. By the 3rd day after operation the sensory loss on the lips had recovered. Normal sensation to the tip of the tongue returned slowly over the next 3 weeks.

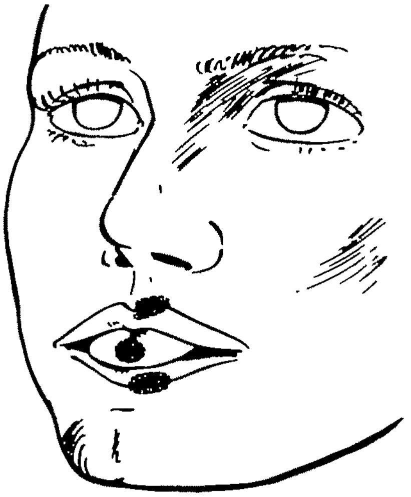

FIG. 1 Areas of diminished sensation to pinprick on the day following operation Taste sensation was unaffected.

DISCUSSION

Injury to the lingual nerve following orotracheal intubation is rare and a search of the literature revealed only three reports in the past 20 yr. On two occasions, right-sided injury was reported (Teichner, 1971; Loughman, 1983) and in one, left-sided injury was described (Jones, 1971). On all occasions difficulty in intubating the trachea was mentioned and, on two occasions, specific mention was made of cricoid pressure being applied. As far as can be ascertained, the present paper is the only one to report bilateral damage to the lingual nerve.

The lingual nerve arises from the posterior division of the mandibular nerve and then passes between the tensor veli palatini and the lateral pterygoid muscles where it is joined by the chorda tympani branch of the facial nerve. This carries preganglionic parasympathetic (secretomotor) fibres supplying (via the mandibular ganglion) the submandibular and sub-lingual salivary glands. The majority of the fibres in the chorda tympani are afferent, carrying taste sensation from the anterior two-thirds of the tongue. Thus, damage to the lingual nerve during intubation may cause loss of taste sensation, as reported by Teichner (1971) and Jones (1971). To date, no instances of sudomotor impairment have been reported.

The lingual nerve passes anterior to the inferior dental nerve, the other main division of the mandibular nerve, and after emerging from the lower border of the lateral pterygoid it lies in contact with the inner surface of the mandible and is covered medially by the medial pterygoid muscle. After emerging from the anterior border of this structure it lies sub-mucosally just inferior to the 3rd molar tooth. The nerve may be injured, particularly on the right side, by direct trauma from the laryngoscope blade either in this position or as it lies on the mylohyoid muscle in the floor of the mouth (Teichner, 1971). Schwartz (1973) has reported that injury of the lingual nerve often accompanies extraction of the 3rd molar tooth and has suggested that in some cases, tongue retraction during operation may cause stretching and injury.

During the terminal part of its course the lingual nerve lies on the lateral border of the hyoglossus muscle. It then passes round the submandibular duct and divides into its terminal sensory branches. During tracheal intubation considerable force may be applied to the base of the tongue (Scheck, 1982). This results in traction, via the hyoglossus, the hyoid bone and the thyrohyoid membrane on the thyroid and cricoid cartilages. If the cricoid is restrained by cricoid pressure or manipulation, the lingual nerve may be stretched and damage may occur.

The inferior dental nerve, the other main branch of the mandibular division of the trigeminal nerve, enters the mandibular canal by passing lateral to the spheno-mandibular ligament. It supplies branches to the teeth and gums and emerges from the mental foramen as the mental nerve. The latter supplies sensation to the skin of the chin, and the skin and mucuos membrane of the lower lip. During difficult intubation, force may be transmitted to the mandible, causing partial forward subluxation of the temporo-mandibular joints and there may be traction on the mandibular nerve as it emerges from the foramen ovale at the base of the skull. This mechanism could account for the decrease in sensation over the lower lip and for the loss of sensation over the tip of the tongue seen in this patient. The fact that taste sensation was intact would also indicate that damage had occurred proximal to the point at which the chorda tympani joins the lingual nerve.

Loss of the sensation of the left upper lip is difficult to explain as this is supplied by the maxillary division of the trigeminal nerve (inferior orbital nerve). It is possible that the presence of a tracheal tube in the nasal cavity could cause compression of nasal branches of the long sphenopalatine and the great palatine nerves which supply sensory branches to the walls and floor of the nasal cavity. It could be postulated that aberrant labial branches might occur from either of these nerves and hence sensory loss would occur over the upper lip.

In conclusion, temporary injury to a number of terminal branches of the trigeminal nerve is described. Most, but not all, of the damage is explicable on anatomical grounds.

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EXTRADURAL BLOOD PATCH – WHY DELAY?

H. QUAYNOR AND M. CORBEY

SUMMARY

Seven patients are described in whom a prophylactic blood patch was instituted within 15 min of accidental dural puncture. Five of the patients received extradural anaesthesia before the blood patch, and one after the blood patch had been performed. In three of these patients further "top-up" doses of local anaesthetic were performed through the extradural catheter. The quality of analgesia obtained was satisfactory. No symptoms of spinal headache occurred in any of the patients.

The use of a blood patch in the management of headache following dural puncture is established practice (Gormley, 1960; Crawford, 1979). Nevertheless, the question remains, at what point should the patch be applied?

We report on seven patients in whom a blood patch was applied prophylactically—immediately after the puncture of the dura.

Of the cases reported, three (patients 3, 5 and 6) were inpatients and were followed up for 1 week. Of the four other patients, Nos 1, 4 and 7 were admitted originally for "day-case" surgery, and patient 2 was a "short-stay" case. This group was asked to report any untoward symptoms or headache occurring during the first week after discharge.

CASE REPORTS

Patient No. 1

A 37-year-old female received lumbar extradural anaesthesia for a varicose vein operation. The extradural puncture was performed in the lateral position at L4–5 with a 17-gauge Tuohy needle. Dural tap occurred at this level. Successful puncture was established at L3–4 and 20 ml of 2% mepivacaine with adrenaline injected. The needle was allowed to remain in position, and 16 ml of sterile autologous blood was injected to the extradural space 7 min later. Blood was also sent for bacterial culture.

The intensity of analgesia to pinprick was assessed at 20 min, and anaesthesia was demonstrated from T10 to S2. The operation proceeded uneventfully. The patient was discharged on the second day after operation without any untoward symptoms.

Patient No. 2

A 33-year-old male underwent extradural blockade for arthroscopy and meniscectomy. An 18-gauge Tuohy needle was used at the L3–4 space with a saline-loaded syringe. The dura was punctured accidentally. A successful extradural block was performed at the L2–3 space, and 20 ml of 2% mepivacaine with adrenaline was injected. Seventeen millilitre of sterile autologous blood was injected through the Tuohy needle at the L3–4 space, and 3 ml of blood sent for culture. At 20 min blockade was complete from T9 downwards. The patient lay flat for the next 18 h, and did not experience any headache. He was discharged on the second day after operation.

Patient No. 3

A 61-year-old female, weighing 55 kg, was scheduled for a total hip replacement. Spinal anaesthesia was performed at the L3–4 space with a 22-gauge needle, using "heavy" amethocaine 12.5 mg with adrenaline 200 µg. Extradural blockade had been planned so as to extend the analgesia into the period after operation. Using a 16-gauge Tuohy

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needle, the dura was punctured accidentally. A catheter was placed successfully via the space above. With the patient still in the lateral position, a blood patch was performed at L3–4, using autologous blood 15 ml under sterile conditions.

When further analgesia was required 2.5 h after the first spinal injection, 0.5% bupivacaine 17 ml was given through the extradural catheter before the conclusion of the operation. This produced adequate analgesia during the remainder of the operation and for the subsequent 6 h. The patient then received morphine 4 mg in saline 10 ml, which produced analgesia lasting another 8 h. The following morning she received 0.25% bupivacaine 12 ml through the extradural catheter, which produced analgesia lasting 4 h. The catheter was then removed. Spinal headache did not occur.

Patient No. 4

A 44-year-old male patient was admitted as a "day-case" for arthroscopy under extradural anaesthesia. Accidental dural puncture occurred at the L3–4 space when using a 16-gauge Tuohy needle. Six millilitre of 0.5% bupivacaine was placed in the subarachnoid space. An extradural blood patch was performed at L2–3 with 17 ml of sterile autologous blood. After 16 h bed rest, the patient was allowed up and was discharged the same day. No headache occurred.

Patient No. 5

A 52-year-old male patient underwent a thromboendarterectomy under extradural analgesia. Using a 16-gauge Tuohy needle the dura was accidentally punctured at the L3–4 space.

Successful extradural placement was obtained at the space above, and 0.5% bupivacaine 20 ml injected through the indwelling catheter. A blood patch was performed at L3–4 with 15 ml of autologous blood. Anaesthesia was evident up to T8 and the operation proceeded without further problem.

In the period after operation the patient received three "top-up" doses of 0.5% bupivacaine 10 ml, each giving analgesia of approximately 4 h duration. He developed no symptoms of post-spinal headache.

Patient No. 6

A 77-year-old thin, asthenic patient underwent a transvesical prostatectomy under extradural anaesthesia. Although care was taken during the procedure, the dura was inadvertently punctured at a depth of approximately 2.5 cm with a 16-gauge Tuohy needle. After a successful extradural blockade had been obtained via the space above (L2–3), 0.5% bupivacaine 17 ml was given through the Tuohy needle before a catheter was introduced to the extradural space. A blood patch was performed at the site of the dural puncture (L3–4) using 17 ml of autologous blood.

Analgesia was complete to T6 and was adequate for the operation.

After the operation, 4 h after the original dose, the patient was given a bolus dose of 0.5% bupivacaine 10 ml and a continuous infusion of 0.25% bupivacaine 6 ml h^{-1} was commenced via the extradural catheter. This was continued during the first 14 h after the operation. He required no further analgesia, and developed no symptoms of spinal headache.

Patient No. 7

A 26-year-old female underwent arthroscopy under extradural anaesthesia. Using an air-filled syringe and the midline approach, the dura was accidently punctured at L3–4 with a 16-gauge Tuohy needle. Successful puncture was obtained at L2–3 and 20 ml of 2% prilocaine with adrenaline injected slowly. The Tuohy needle was allowed to remain in position at L2–3 and, 6 min after the extradural injection had been completed, 17 ml of autologous blood was injected. Anaesthesia, assessed after 20 min, showed a sensory level to pin-prick from T6 to L5, with incomplete sensory loss at S1 and S2. Likewise, there was an incomplete motor blockade at the ankles. The operation proceeded without any further analgesic. The patient was treated lying flat for 18 h and was mobilized on the day after the operation. She was discharged the same day without symptoms of spinal headache.

DISCUSSION

Bromage (1978) quotes an incidence of post-spinal headache of 70–80% with the use of 16–18 gauge Tuohy needle. Infusions of saline to the extradural space have been used to treat such headache. Crawford (1972) used a continuous infusion of Hartman's solution via an extradural catheter, and was able to prevent post-spinal symptoms in the majority of his patients. Such therapy attempts to maintain a high extradural pressure so as to decrease the rate of leakage of cerebrospinal fluid into the extradural space. Since the saline is absorbed rapidly, continuous infusion is necessary.

The "blood patch" attempts to seal the leak, and the low incidence of complications in both short- and long-term follow-up of extradural blood patch (Abouleish, 1975) has prompted its widespread acceptance.

When injected through an indwelling catheter, the blood patch appears to be rather unsuccessful (Palahnuik and Cumming, 1979; Crawford, 1980). In all the patients reported by us, the blood patch was given through the extradural needle, which was placed either at or one space above or below the site of the dural puncture. This would appear to ensure that the blood is deposited at a level that is not too remote from the site of the dural opening.

One factor influencing the extent of spread of fluid within the extradural space is the volume injected. Therefore, we chose to use a volume of 15–20 ml of blood. Crawford (1980) has reported a higher failure rate when using smaller volumes of blood. Loeser and colleagues (1978), using 10 ml of autologous blood, have reported a very high failure rate (71%) when prophylactic blood patch was performed within 24 h of the dural puncture. Although they do not mention the site of injection or the precise timing of the blood patch, the efficacy of the extradural "patching" with 10 ml may be influenced by the presence of local anaesthetic in the extradural space.

Six of the reported patients received extradural anaesthesia after dural puncture had occurred. In the four patients to whom extradural anaesthesia was given through the extradural needle (patients 1, 2, 6 and 7) an initial test dose was not given before the full dose. Approximately 20 ml of anaesthetic solution was injected at a level removed from the site of the dural puncture. We felt that, with a slow rate of injection, the increase in pressure within the extradural space would be unlikely to exceed that of the subarachnoid space at the site of the dural puncture. Thus, it would be unlikely that anaesthetic solution could be "pushed" through the hole in the dura.

On the six occasions when extradural anaesthesia was performed after dural puncture, using approximately 20 ml of local anaesthetic, the onset, quality and duration of blockade did not resemble that normally associated with spinal anaesthesia, that is rapid onset, complete motor paresis, and a prolonged duration of effect.

Marx (1979) stated that the placement of an extradural blood patch through the initial needle "entails abandonment of regional anaesthesia". In five of the cases reported, where blood patching was performed after the initial block, the analgesia was unaffected by the presence of the blood. Furthermore, in three of the patients (3, 5 and 6) extradural bupivacaine was given through the catheter after the initial blood patch, and further "top-ups" were repeated after the operation. The duration and effect of these subsequent "top-ups" were in accord with what one would expect with a normal block. This is in agreement with the case reported by Christensen and Lund (1983).

Crawford (1980) has argued against prophylactic blood patch because "continuous extradural infusion is effective in 85 per cent of cases". However, blood patching, with its almost 100% success and its safety, would appear to be the treatment of choice, and its prophylactic use surely has its place, especially in an increasing ambulant surgical population, since the overall hospital stay is not prolonged substantially.

In conclusion, we feel that immediate blood patch through the extradural needle, using at least 15 ml of autologous blood, is a simple and effective prophylactic therapy against post-dural headache after accidental dural punction. The quality of anaesthesia obtained does not appear to be influenced by the early administration of the blood patch, and subsequent continuous or intermittent "top-up" techniques appear to be similarly unaffected.

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CORRESPONDENCE

CUTANEOUS REACTIONS TO ATRACURIUM

Sir,—Many anesthetists have commented on the incidence of cutaneous reactions following the administration of atracurium (Mirakhur et al., 1983; Rowlands, 1983). Some have speculated that these reactions may be the result of histamine release (Philbin et al., 1983). However, a recent study concluded that atracurium has a low potential for causing histamine release and that the clinical signs observed following atracurium do not correlate well with plasma histamine concentrations (Barnes et al., 1984).

In an attempt to elucidate the mechanism of these cutaneous reactions we have assayed plasma for conversion of the C3 component of complement in eight female patients given atracurium 0.3–0.6 mg kg^{-1}. The patients were premedicated with oral lorazepam and anaesthesia was induced with fentanyl 2–5 μg kg^{-1} and a "sleep" dose of thiopentone. Venous blood was sampled immediately before and 2 min after giving atracurium. Six patients had a cutaneous reaction, but no patient showed any evidence of C3 conversion.

We conclude that complement conversion is not involved in the production of flushing in the majority of patients who react in this way following atracurium.

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ANAESTHESIA FOR FRACTURED HIP

Sir,—The article on subarachnoid and general anaesthesia for fractured hip (McKenzie, Wishart and Smith, 1984) is an important contribution to the literature in this area. In their series they demonstrated that the mortality at 14 days was significantly less in the subarachnoid group, but no difference existed at 1 year. They concluded that subarachnoid anaesthesia plays no part in decreasing the burden which this disease places in health care resources.

I believe the authors are selling themselves short. There are many possible causes of death during the year following a fractured hip, from surgery and anaesthesia-related causes in the early perioperative period to causes more related to the patient's often underlying pathology. The authors have shown that they can prevent many of the early deaths. One piece of the jigsaw puzzle has been put into place. The fact that the later deaths could not be prevented should not be an admission of failure. For example, penicillin undoubtedly decreases the mortality in septuagenarians during a bout of pneumococcal pneumonia compared with no antibiotic treatment. However, if it were found that there was no significant effect on mortality at 1 yr, I doubt if we would stop using the drug or conclude that it was of no use in the disease.

In this study the principle of reduction in early mortality is the important issue. This raises other important questions. It holds true also in young, healthy patients with hip fractures or in patients having elective hip surgery (who have better long-term prognosis). Might not this early reduction in mortality indeed confer a long-term benefit?

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REFERENCE

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AIRWAY OBSTRUCTION—AN UNUSUAL PRESENTATION

Sir,—Obstruction of endotracheal tubes and their connectors by foreign bodies has been documented extensively. Among the items responsible have been hardened KY jelly (McLellan, 1975), tumour fragments (Barat, Ascorve and Avello, 1976), Blenderm tape (Jago, Johnstone and Restall, 1977) and the plastic sheath from a disposable needle (Wittman, 1982). The blockage has usually become apparent very quickly because of airway obstruction. We wish to report an instance with the unusual presentation of acute hypotension.

A 73-year-old man was anaesthetized for cystoscopy with thiopentone followed by nitrous oxide, oxygen and enflurane breathed spontaneously via a face mask and Bain system. After 30 min the surgeon decided to proceed to retropubic prostatectomy. Atracurium 40 mg i.v. was given and the trachea intubated with a 9-mm cuffed endotracheal tube with a Cobb's connector. Manual ventilation required high inflation pressures, but both sides of the chest were seen to be moving and air entry was heard on auscultation. Ventilation was continued using a Manley ventilator.

At this point, the systolic arterial pressure was observed to decrease rapidly from 90 to 50 mm Hg and remained low despite the rapid infusion of crystalloid. The Manley began to "hiccup" and, on revertion to manual ventilation, inflation proved impossible. The endotracheal tube was changed immediately, ventilation was reinstituted with ease, and the arterial pressure returned to its former value. Examination of the discarded tube and connector revealed that a plastic spigot from the air seal of the face mask was wedged in the corrugations of the catheter mount in such a manner that a one-way valve effect was produced.

Inflation of the chest was possible, but expiration was not. The subsequent increase in intrathoracic pressure was clearly responsible for a decrease in venous return and decreases in cardiac output and arterial pressure. Similar effects have been reported by Mason and Tackley (1981) in the Intensive Care Unit when exhaled blood caused a blockage of the expiratory filter on a Cape ventilator.

Checking equipment before use should be mandatory. Boulton (1982) has suggested passing an introducer or bougie through endotracheal tubes before use, as is common practice in North America. However, in this case the obstruction would only have been revealed had the bougie passed through the catheter mount as well.

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SIMPLE ATRACURIUM INFUSIONS

Sir,—In most surgical operations requiring the use of neuromuscular blocking agents, satisfactory muscle relaxation is maintained by incremental doses without the use of a peripheral nerve stimulator. When using atracurium, relaxation wears off rapidly once it starts to do so, and incremental doses—which may be required at 15–20 min intervals—must be given immediately to maintain smooth operating conditions.

Eager, Flynn and Hughes (1984) have shown that atracurium infusions can be used successfully for long surgical procedures using sophisticated equipment for peripheral nerve stimulation and for monitoring neuromuscular blockade. As such equipment may not be available in many hospitals, 55 patients whose operations were expected to last at least 90 min received an atracurium infusion, neuromuscular blockade being monitored using a hand-held peripheral nerve stimulator (Isleworth Electronics) in seven patients and on purely clinical grounds in the remainder. Seventeen of the patients were older than 70 years, 18 were ASA grade 3, three were ASA grade 4 and one was ASA grade 5. A bolus dose of atracurium 0.5–0.6 mg kg^{-1} was given to facilitate tracheal intubation; an infusion i.v. of atracurium 0.5 mg ml^{-1} in 0.9% sodium chloride B.P. using a Soluset paediatric infusion set was used in six patients, and an infusion of 5 mg ml^{-1} using a Grazeby Dynamics M S. 16 syringe driver in the remainder.

The infusion was commenced at a rate of 0.4 mg kg^{-1} h^{-1} approximately 20–30 min after the start of the anaesthetic, as atracurium has a half-life of about 25 min, and was increased or decreased, as required, and discontinued at closure of the peritoneum in patients undergoing intra-abdominal surgery and at an estimated 15 min before the end of the operation in the others. All patients received droperidol 5 mg and fentanyl 0.1–0.4 mg during anaesthesia.

In the seven monitored patients, the infusion rates varied from 0.35 to 0.66 mg kg^{-1} h^{-1} (mean 0.48) and lasted from 31 to 285 min. Spontaneous respiration returned between 5 and 21 min after the infusion had been discontinued, 4 min after neostigmine 2.5 mg had been given on two occasions and at or before the neostigmine in the remainder.

In the 48 non-monitored patients, the infusion rate varied from 0.36 to 0.86 mg kg^{-1} h^{-1} (mean 0.50) and lasted from 25 to 240 min. Spontaneous respiration returned between 5 and 40 min after the infusion had been discontinued, before the neostigmine (which was omitted four times) in 18 patients, and in 4 min or less after the neostigmine in all except three patients. The doses of atracurium used in these infusions are greater than those used by Eager, Flynn and Hughes (1984), possibly because less fentanyl was used and none of the patients was given halothane. There were no problems with reversal, even in those patients where a change in surgical plan at operation resulted in a shorter procedure than expected. I have found that an atracurium infusion can be safely used without monitoring neuromuscular blockade.

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REFERENCE

Eager, B. M., Flynn, P. J., and Hughes, R. (1984). Infusion of atracurium for long surgical procedurs. *Br. J. Anaesth.*, **56**, 447.

Sir,—We would agree with Dr Rowlands' finding that atracurium can be safely infused without the use of sophisticated monitoring equipment; indeed, such was the ultimate aim of our study.

However, in order to determine the rate of infusion needed to produce a suitable level of neuromuscular blockade, a quantitative assessment using such apparatus was made. The use of a syringe pump would obviously be safer with regard to control of the amount of drug infused, but we have also found paediatric infusion sets to be quite satisfactory. Such infusion sets are more generally available than syringe pumps.

If a peripheral nerve stimulator is not used there is a possibility of administering more atracurium than is absolutely necessary in order to ensure full surgical relaxation throughout the procedure. In our study we found that the level of block varied according to the degree of surgical stimulus. The difference in mean infusion rates between Dr Rowlands' and our study would appear to result from the different anaesthetic techniques used, as he suggested.

Finally, Dr Rowlands shows once again the usefulness of atracurium in geriatric and medically compromised patients. This continues to be one of the main indications for the use of this drug in our clinical practice.

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INTERCOSTAL BLOCKADE

Sir,—Much concern has arisen regarding the spread of local anaesthetic drugs during intercostal nerve blockade. Moore, Bush and Burnett (1980) and Moore (1981) found that, when 3–5 ml of solution was *accurately* placed into the costal groove of a rib, its spread was limited to the groove to which it was injected. On the other hand, Murphy (1984) and Nunn and Slavin (1980) found a much more extensive spread—that is, behind the parietal pleura over two to five ribs or their interspaces. In one instance (Murphy, 1984), however, the dye spread as in our studies—that is, "in one intercostal plane only."

Careful examination of the photographs in our studies (Moore, Bush and Burnett, 1980; Moore, 1981), compared with those of Murphy (1984) and Nunn and Slavin (1980), leaves no doubt that the spread of the India ink differs. Murphy also stated, "By pushing the parietal pleura forward, the dye was spread easily subpleurally to reach the intercostal space above and below the one cannulated." The question arises, therefore, what or who did the pushing? I agree with Murphy (1984) that, "A possible explanation for the discrepancy may be that, in Moore's studies, injections of dye may not have pierced the posterior intercostal membrane and were bound by this sturdy structure." We accept the fact that in our technique the solution in *accurately* placed into the groove in the rib. In their studies, the barriers which limit spread (posterior intercostal membrane and the endothoracic and subserous fascia) appear to have been pierced or disrupted by (1) removal of the thorax of the cadaver (Nunn and Slavin, 1980) (2) too deep an insertion of the needle (Nunn and Slavin, 1980); Murphy, 1984), (3) the insertion of a 16-gauge Tuohy needle which has a 4–5 mm bevel, the insertion of plastic tubing, the injection of 20 ml of solution (Murphy, 1984), or all of these; or (4) trauma, for example, fractured ribs (Murphy, 1983).

While the technique which we use has resulted in complete sensory and motor blockade in more than 15 500 patients for surgery as well as for the relief of pain after operation (Moore and Bridenbaugh, 1962; Moore, 1975; Moore et al., 1978), Murphy (1983) admits that his method of continuous intercostal nerve block is satisfactory only for pain relief after operation. He states, "Attempts at assessing the number of dermatomes blocked using this technique met with failure. Most patients appreciated no difference in pinprick sensation between the dermatomes on either side of the body. Some patients experienced hyperaesthesia over the dermatomal distribution of the gall bladder." Also, unlike our technique, Murphy (1983) admits his does not relieve pain in all patients and states: "Of the patients studied, 92% and 76% required no additional analgesia in the first 24 h and first 48 h following operation, respectively."

My primary concern, however, is not understanding how postoperative pain mediated by the intercostal nerve is relieved, but rather keeping to a minimum the complications from the technique of intercostal nerve block. Continued complications from intercostal nerve block could lead to criticism and abandonment of the block. My colleagues in the U.K should not forget the recent rebirth of regional anaesthesia in the U.K. after the Woolley–Roe spinal anaesthesia case (Medicine and Law, 1953; Medico-Legal, 1954). A significant number of problems with a specific regional block could have a similar effect. Likewise, they should be aware that little was written in the U.K. about the advantages of intercostal nerve block until the article of Nunn and Slavin (1980). Also, they should be aware that a U.K. surgeon (Chivers, 1946) reported a 19% incidence of pneumothorax from intercostal nerve block, which has been cited repeatedly to condemn the technique.

Residents in anaesthesia perform 95% of the intercostal nerve blocks using the technique which we advocate, and minimal complications have resulted (Moore, 1975). On the other hand, whether Murphy's technique (1983) of relieving postoperative pain of cholecystectomy is without serious complications in the hands of the inexperienced remains to be reported. Evidently in experienced hands, it has resulted in: (1) "the integrity of the parietal pleura being broken in 5 instances" (Murphy, 1984); (2) massive flank haematoma in one (Baxter, Flynn and Jennings, 1984), and (3) the tubing penetrating the parietal pleura in three examples (Baxter, Flynn and Jennings, 1984). Also, I have observed one patient in whom a small artery was lacerated when the anaesthetist attempted to place plastic tubing into the subclavian vein using the subclavicular approach and a 16-gauge needle. Bleeding from the artery peeled the parietal pleura from the ribs and eventually collapsed the lung. To stop the bleeding and re-expand the lung required 3.5 h of surgery. Therefore, one wonders whether this might also occur if: (1) the 16-gauge Tuohy needle lacerated an intercostal blood vessel (Baxter, Flynn and Jennings, 1984), particularly the artery; (2) the needle pierced the fascial barriers; and (3) the plastic tubing maintained a path for blood to escape behind the pleura.

Finally, Murphy (1983) stated, "The intercostal blockade was then 'topped' up by the anaesthetist with the same volume and concentration of drug." Where was this done, what precautions were taken to treat a systemic toxic reaction with convulsions if one occurred, and what were the anaesthetist's credentials (consultant, registrar, etc.)? Bupivacaine, the drug advocated by Murphy (1983), cumulates, as do all amide derivatives (Moore et al., 1978), and plastic tubing can migrate into a blood vessel (Ravindran, Albrecht and McKay, 1979). Therefore, systemic toxicity is more likely to occur with "top-up" doses than with the initial dose. Furthermore, with intercostal nerve block, peak bupivacaine blood concentrations are higher and occur more rapidly than with most other regional block techniques (Moore et al., 1978). Heath (1982) and Kelly and Henderson (1983) have pointed out the necessity of having a knowledgeable physician administer regional blockade. Hopefully, if the "top-up" dose of bupivacaine 100 mg (Murphy, 1983) was done in the patient's room, it was done by such a person with equipment (oxygen, bag, mask, airways, etc.) and drugs to treat a systemic toxic reaction within arm's reach and readied for immediate use before the "top-up" injection. Otherwise, an occasional catastrophe, that is, systemic toxicity with cardiac arrest, encephalopathy, or death, is likely to occur (Heath 1982, 1983).

To conclude, from a clinician's standpoint, exactly how intercostal nerve block relieves postoperative pain makes little difference, but serious complications from the block do, for they could lead to the abandonment of a valuable technique.

DANIEL C. MOORE
Seattle

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Ravindran, R., Albrecht, W , and McKay, M (1979). Apparent intravascular migration of epidural catheter. *Anesth. Analg*, **58**, 252.

Sir,—While I consider it highly unlikely that I will ever achieve a level of experience in regional anaesthesia comparable to that of Dr Moore, I am nevertheless glad of this opportunity to reply to his letter, since I find that he has both misinterpreted and misquoted a number of points in my recently published papers on continuous intercostal nerve blockade (Murphy, 1983a, 1984).

In emphasizing the accurate placement of his needle, Dr Moore has clarified why his results have differed from mine and those of Nunn and Slavin (1980). Dr Moore clearly does not wish to inject his solution deep to the posterior intercostal membrane, whereas this is our expressed goal As demonstrated in one instance in my cadaveric study (Murphy, 1984), an extradural catheter *incorrectly* placed superficial to the posterior intercostal membrane gave a spread of solution similar to that found by Moore (1981).

Dr Moore states that I "admit that (my) method of continuous intercostal nerve block is satisfactory only for post-operative pain relief". This is not true. I have successfully used this method of intercostal blockade to induce *complete* analgesia in patients with up to eight unilateral fractured ribs (using a single intercostal cather). These results have been published elsewhere (Murphy, 1983b). Furthermore, Dr Moore has misinterpreted my statement that "92% and 76% (of patients) required no additional analgesia in the first 24 h and first 48 h following operation" This does not imply that the block was ineffective in 8% and 24%, respectively, but rather refers to the development of tachyphylaxis to the local anaesthetic used. In fact I have stated that "On subsequent questioning, many patients expressed a preference for the intercostal analgesia" (Murphy 1983a).

Dr Moore states that his primary concern is in the minimization of complications from the valuable technique of intercostal blockade and indeed has published unsurpassable evidence to attest the safety of this block (Moore, 1975). I find it inconsistent, therefore, that he should feel the need to quote a *surgeon* of lesser experience in outlining the hazards of the block or a *case report* of the hazards of subclavian vein cannulation. I would venture to suggest that insertion of an extradural catheter to a single intercostal space is less likely to induce a pneumothorax than multiple injections with smaller needles using the conventional technique.

It is unfortunate that, in further criticism of the new method of intercostal blockade, Dr Moore quotes Baxter, Flynn and Jennings (1984) who did not perform the technique as originally described and misquotes me in saying that "the integrity of the parietal pleura (was) broken in five instances" (Murphy 1984) What I actually wrote was that the pleura was broken "following the division of pleural adhesions and removal of the thoracic viscera", and clearly not in the act of insertion of the intercostal catheters.

I share Dr Moore's concern for systemic absorption of and danger of toxicity from repeated doses of local anaesthetics Indeed, this was the only reason why patients satisfied with their intercostal block, had this form of analgesia discontinued. My criteria for safety with "top-ups" of intercostal catheters were no less stringent than those found acceptable by the Central Midwives Board relating to extradural catheter top-ups administered by midwives working alone.

Finally, I agree with Dr Moore that "from a clinician's standpoint, exactly how intercostal nerve block relieves postoperative pain makes little difference" but then, a study on cadavers was surely never meant to.

D. F. MURPHY
Dublin

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pH AND ATRACURIUM

Sir,—Drs Flynn, Hughes and Walton (1984) have produced an interesting paper on the effects of cardiopulmonary bypass, hypothermia and atracurium. In the discussion it is stated that the inactivation of atracurium is mainly dependent on temperature and pH. However, no pH value is reported in the paper.

There is some controversy as to whether the blood-gas measurements should be reported as measured at 37 °C, or corrected for temperature (Ream, Reitz and Silverberg, 1982; Ashwood, Kost and Kenny, 1983), although at the moment it is almost a "no-contest". Was the carbon dioxide content held constant during hypothermia in these patients? Two patients began to breathe during the bypass procedure and this could indicate, from personal experience, that the pH was not normal utilizing *uncorrected* values. Following the scheme as exhibited by ectotherms, there is evidence that the myocardial, cerebral and renal perfusion is better, thus facilitating even body cooling and obviating the necessity to correct increasing base deficits (Becker et al., 1981; Swain, White and Peters, 1984).

Because of the large difference in pH which can arise depending upon which scheme of reporting is used—7.40 or 7.58—it behoves each investigator in the field of hypothermia to report whether the results are corrected for temperature, or not, as this may have profound implications on drug pharmacokinetics and pharmacodynamics.

D. T. BOLTON
Utrecht

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Swain, J. A., White, F. N., and Peters, R. M. (1984). The effect of pH on the hypothermic ventricular fibrillation threshold. *J. Thorac. Cardiovasc. Surg.*, 87, 445.

Sir,—Dr Bolton raises the pertinent question of the effect of pH changes on the inactivation of atracurium. *In vitro* studies with atracurium showed that a decrease from a pH of 7.4 by 0.2 units increased the half-life of the drug 1.5-fold (Merrett, Thompson and Webb, 1983). However, studies in man showed that respiratory-induced changes in pH from 7.25 to 7.56 produced no consistent effect on the level of neuromuscular blockade nor on the rate of recovery (Payne and Hughes, 1981). These investigators did not study the effects of metabolic acidosis in man. Patients with renal and hepatic failure are known to have varying degrees of metabolic acidosis. The study by Hunter, Jones and Utting (1982) showed no difference in the duration of action of atracurium between anephric and normal patients. Furthermore, Ward and Neill (1983) found no increase in the half-life of atracurium in patients suffering from hepatic and renal failure.

Temporary alterations in pH occur often during cardiopulmonary bypass. In our study, correction of abnormalities of temperature-corrected blood-gas results were undertaken in the usual way with values being restored to the "normal range" as soon as possible. In the two patients who started to breathe spontaneously while on bypass at core temperatures of 25 °C and 28 °C respectively, the $P\mathrm{CO}_2$ and 4.3 and 7.3 kPa, pH was 7.5 and 7.1 and base deficit was +1.3 and −12.5. The latter was corrected with appropriate amounts of sodium bicarbonate. No conclusions could be drawn in view of the differences in acid–base status between the two patients.

Our study was essentially a clinical one intended to assess the feasibility of administering atracurium by infusion for cardiac surgery and to determine the rates of infusion required during cardiopulmonary bypass with induced hypothermia. In our view, changes in pH during hypothermia could possibly affect the pharmacokinetics of atracurium, but it would be difficult to separate these from the effect of hypothermia on the rate of inactivation of the drug and on neuromuscular function.

P. J. FLYNN
B. WALTON
R. HUGHES
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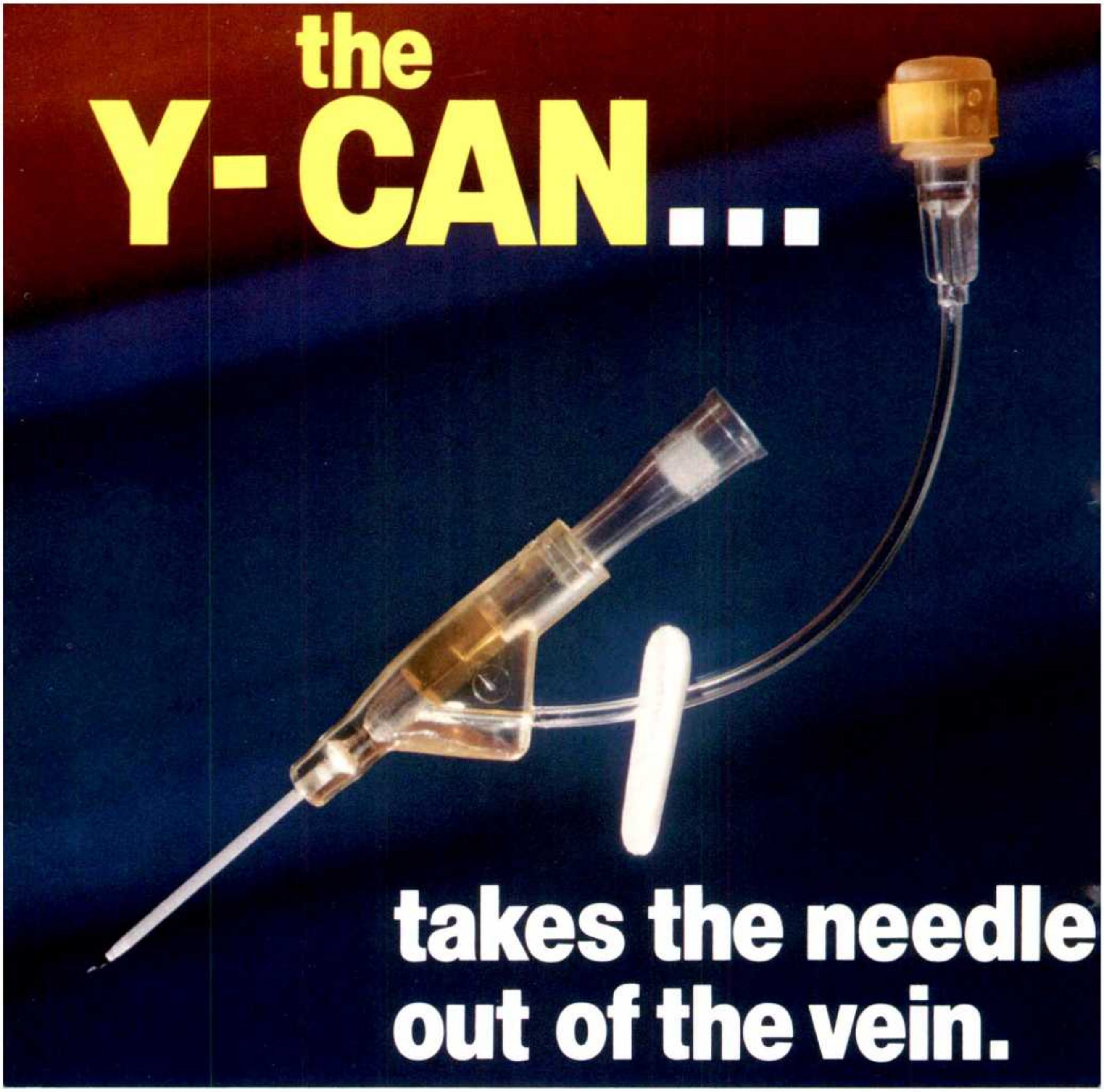

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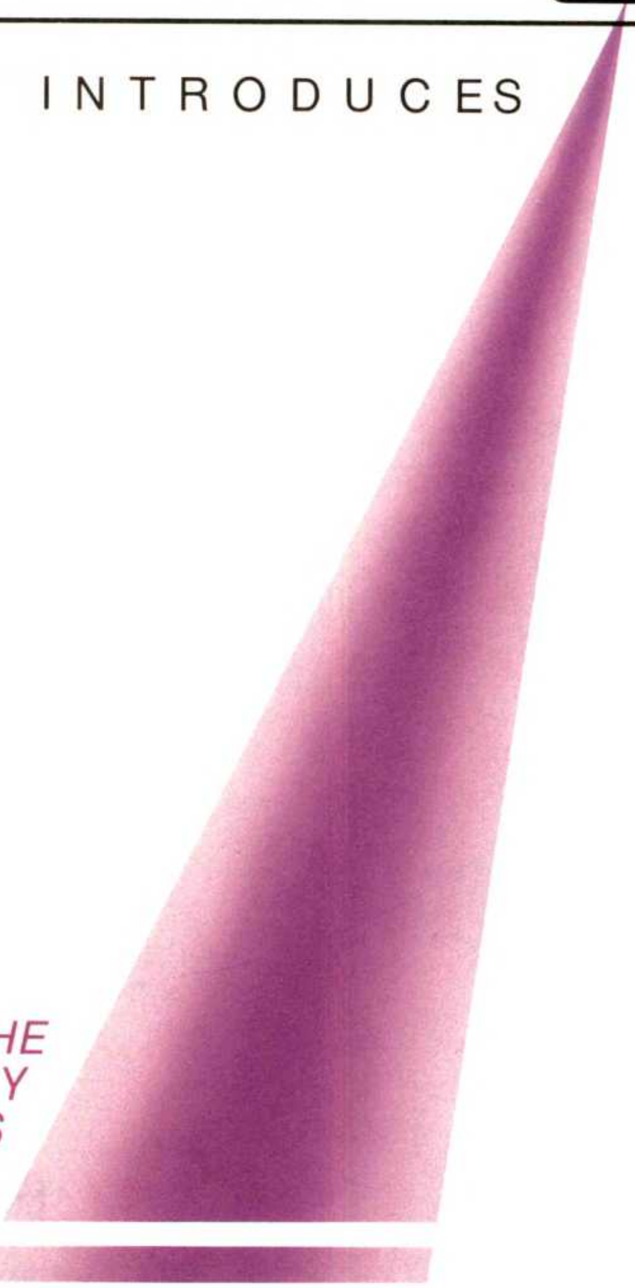

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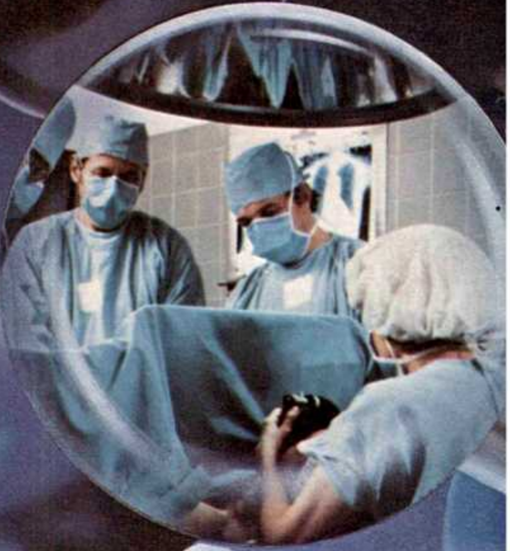

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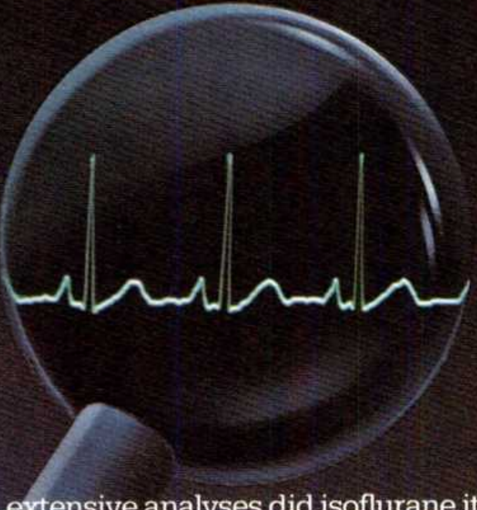

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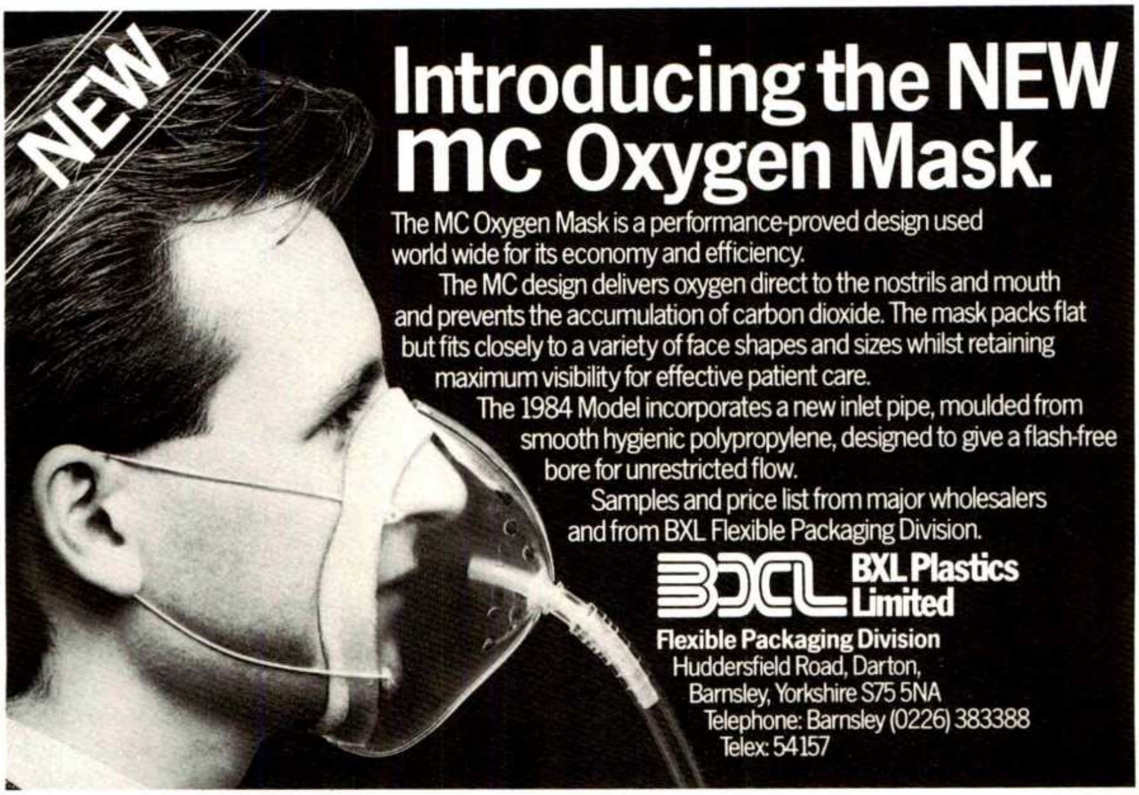

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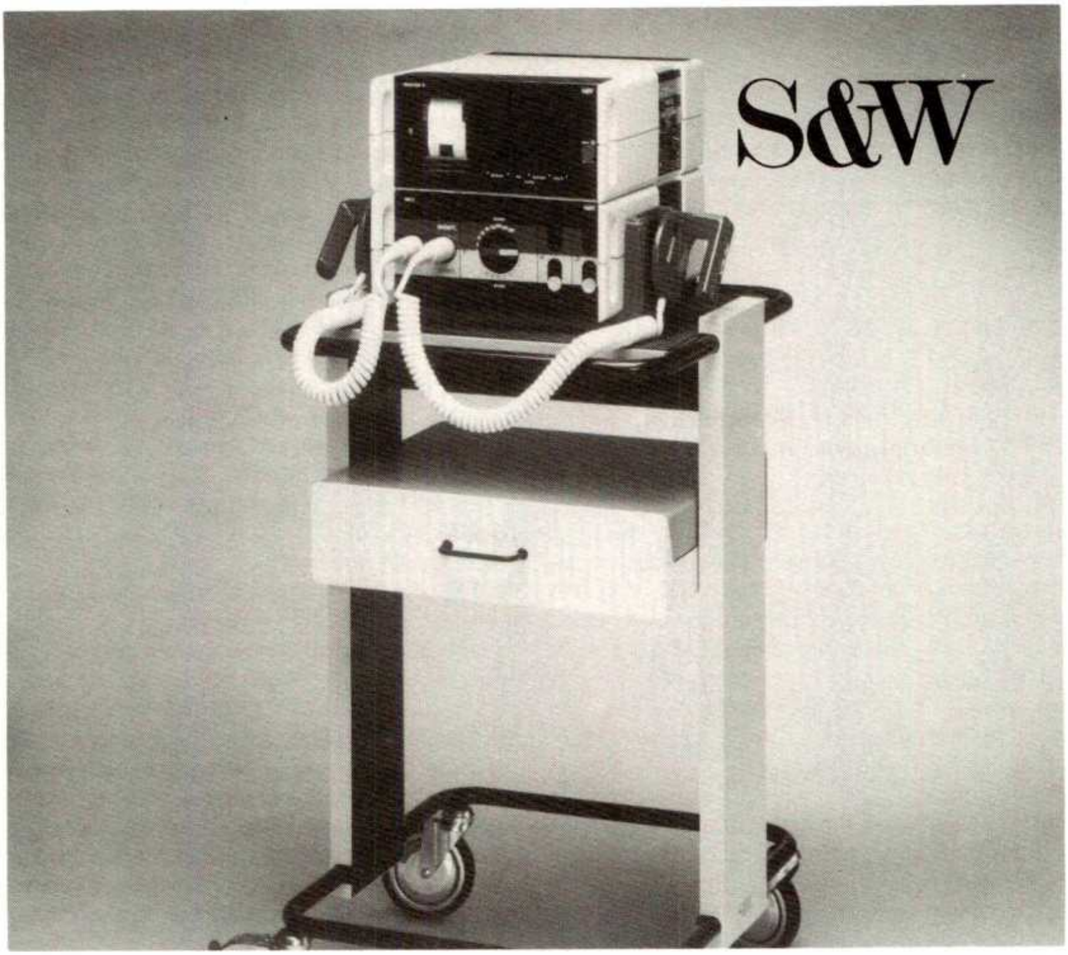

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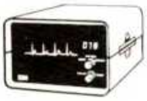
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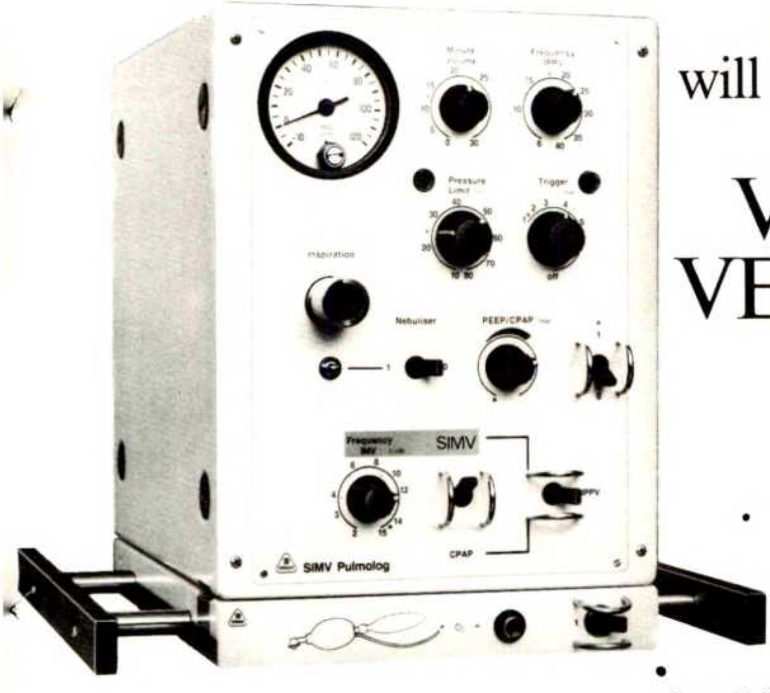

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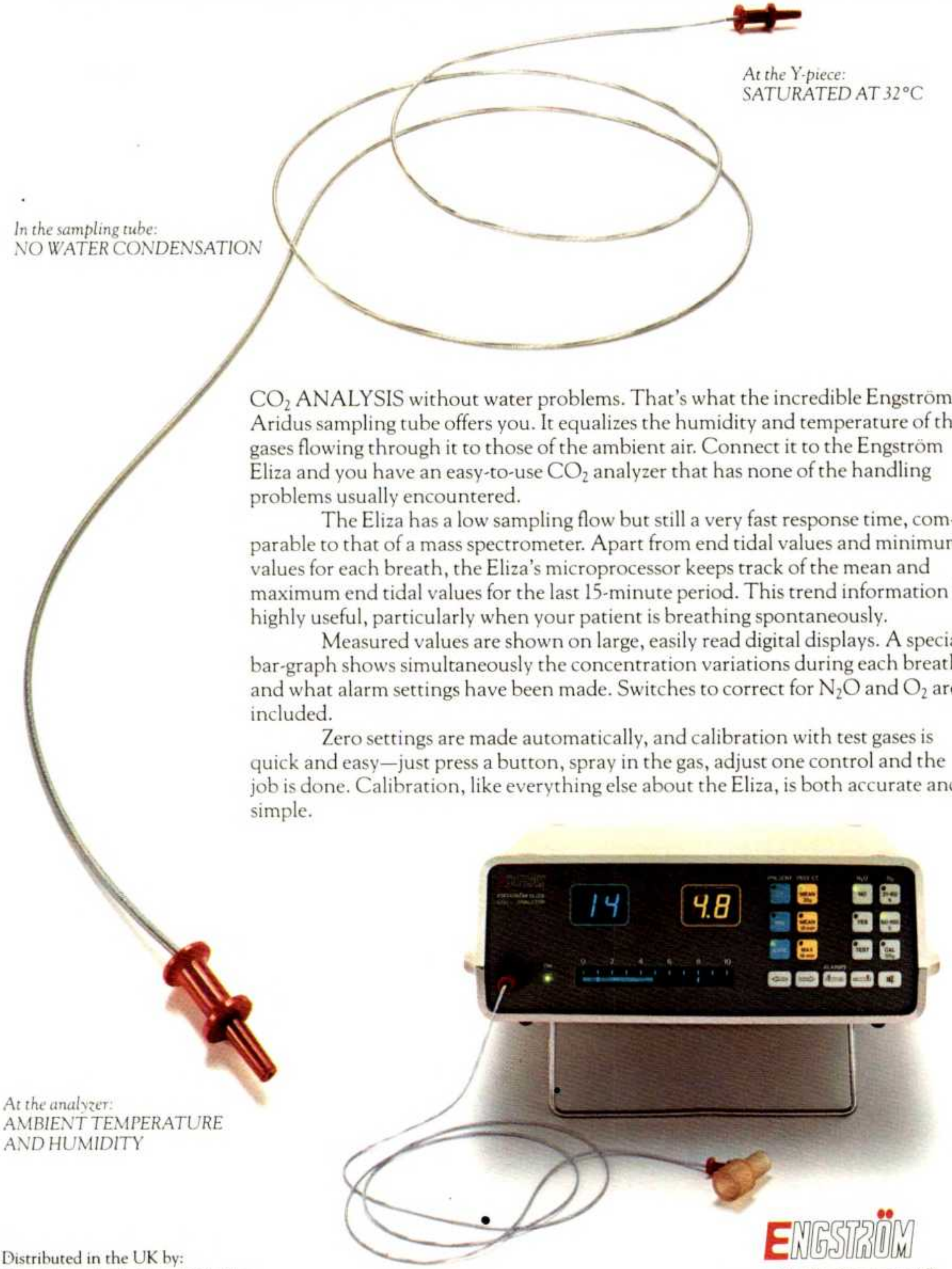

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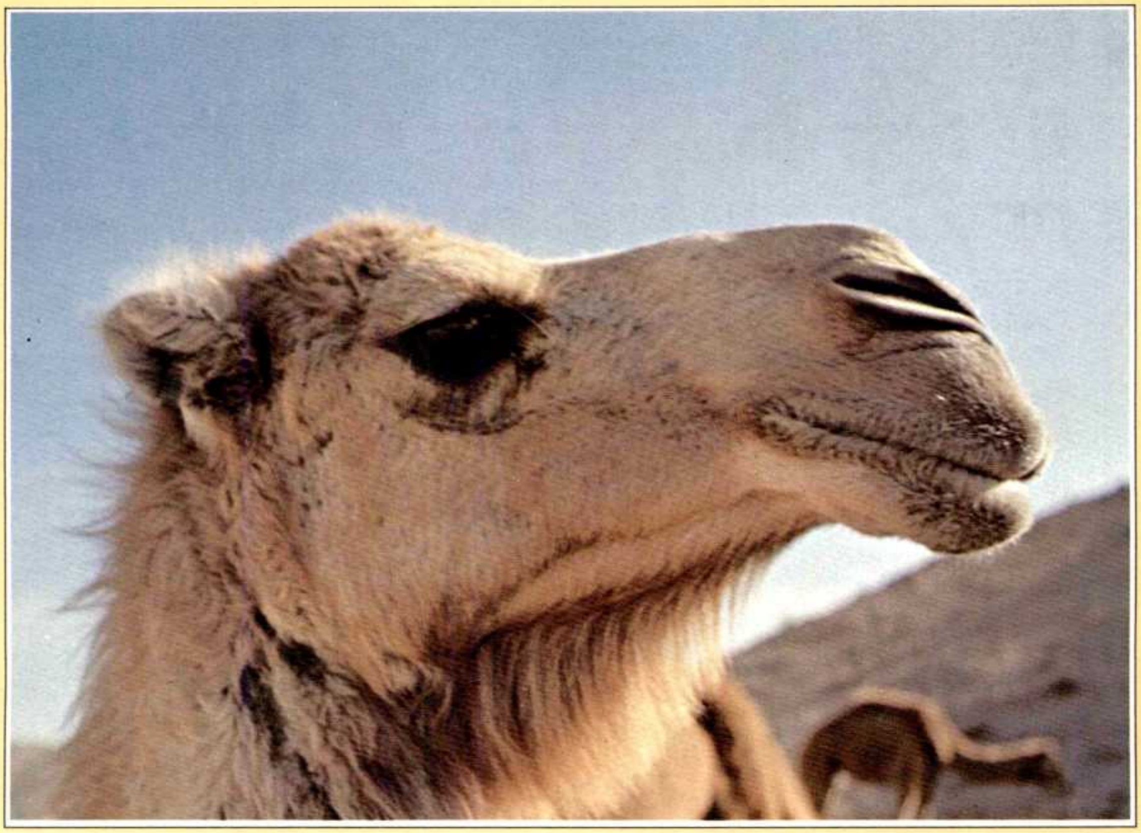

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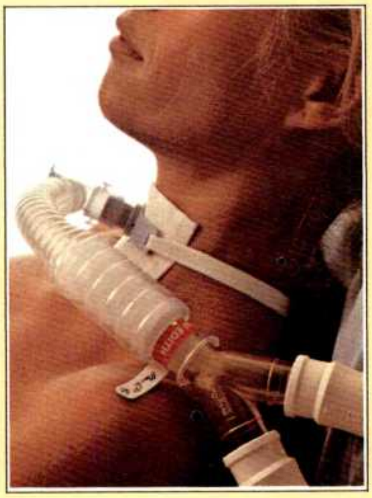

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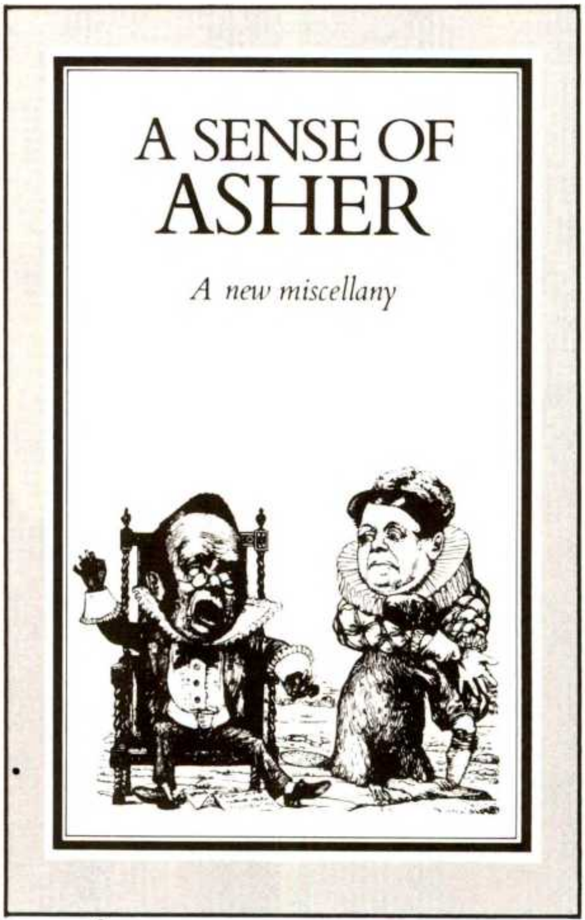

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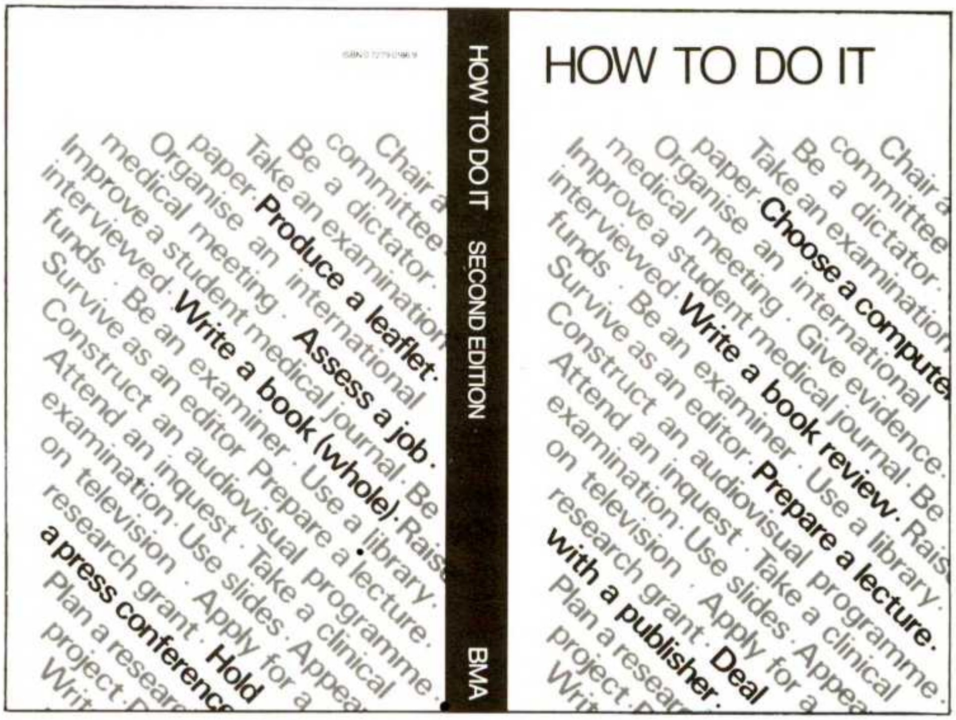
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EDITORIAL

NALOXONE – PARADOX OR PANACEA?

Naloxone, the n-allyl derivative of oxymorphone, has gained widespread use in anaesthesia for the purpose of antagonizing opioid-induced respiratory depression and sedation. Although naloxone has been regarded traditionally as a pure opioid antagonist without agonist activity, following the discovery of the endogenous opioid system (originating with Hughes and his colleagues (1975)) evidence has accumulated to suggest that this may not be so. Within anaesthetic practice, the prime indication for the use of naloxone is the presence of unwanted opioid effects, predominantly respiratory depression in the immediate postoperative period. However, it is well known that the offset of clinical effect seen after a single bolus of naloxone is rapid and usually occurs within 30 min following a typical dose of 0.1–0.4 mg i.v. This clinical duration of action mirrors the decay in plasma concentration which is most rapid over the first 30 min following i.v. administration, although the terminal elimination half-life is approximately 150 min (Aitkenhead et al., 1984). Thus, in order to prevent the re-emergence of opioid agonist effects, it has been suggested that either supplementary doses i.m. or an infusion i.v. should be administered to prolong the duration of opioid antagonism.

Recent information has suggested the need for caution in the use of naloxone by i.v. bolus. There have been reports of ventricular dysrhythmia (Andree, 1980), hypertension (Azar and Turndorf, 1979), and pulmonary oedema (Flacke, Flacke and Williams, 1977) following naloxone 0.4 mg i.v. More recently, two cases of acute pulmonary oedema have been reported after 0.1 mg i.v. in healthy young patients (Prough et al., 1984). It is likely that in all these reports the underlying mechanism comprised acute arousal leading to centrally-mediated catecholamine release, with neurogenic pulmonary oedema in the most extreme cases.

In the light of these reports we suggest that, when tempted to use naloxone i.v. to reverse opioid effects, the anaesthetist should administer the drug slowly in dilute form in order to titrate the minimum dose possible against the result required. In the less acute situation, the i.m. route may be safer.

After the administration of opioids by the subarachnoid or extradural routes, respiratory depression may occur following a variable latent period (3-18 h). This may be treated successfully by the parenteral administration of naloxone, but repeated doses may be necessary. In contrast to its use following parenteral opioids, naloxone does not appear to reverse the analgesic component of extradural/subarachnoid opioids. This is thought to be the result of the high local concentration of opioid in proximity to spinal cord opioid receptors, while the receptors which affect respiratory control are more cephalad—in the region of the brainstem. Cousins and Mather (1984) have suggested that circulating CSF concentrations of opioids around this site are of paramount importance in the mechanism of respiratory depression following subarachnoid or extradural opioid administration.

Since 1975, at least four sub-types of opioid receptor—mu, kappa, sigma and delta—have been defined in the central nervous system (Yaksh, 1984), but these may be only a fraction of those to be discovered in the future. Although it is still not possible to identify those specific effects which result from stimulation of individual receptors, there are clear actions associated with some receptor sub-types, for example, analgesia appears to be mediated via the mu/kappa system and dysphoria is thought to be sigma-mediated.

Naloxone binds competitively to opioid receptors and thus occupation of the site by an agonist (either endogenous or exogenous) is prevented, although this is dependent on the local concentration of each agent at the biophase. It is of particular significance, however, that the affinity of naloxone for each receptor population is not equal, the binding of naloxone to mu sites being very much stronger than to kappa or delta. These specificities are relative, rather than absolute, and it is known that in high local concentrations binding to non-preferred sites can occur.

In addition to the antagonism of opioid-induced respiratory depression and sedation, naloxone has been used therapeutically in the treatment of hypotensive states, stroke, spinal cord injury and other miscellaneous conditions. This may seem paradoxical at first sight for an agent viewed traditionally as a pure opioid antagonist.

In hypotensive states it has been shown in animal models that naloxone increases arterial pressure in both endotoxic and hypovolaemic shock. Some reports have confirmed a similar effect in patients (Peters et al., 1981), although the effect was not observed in patients who were hypoadrenocorticotrophic or receiving high-dose corticosteroids, which indicates that pituitary beta-endorphin plays a role in the hypotensive state (see review by Pinnock (1985)). Weisglass (1983) has shown that naloxone does not produce its effect by a direct action on the myocardium and the following mechanisms have been proposed: centrally mediated increase in sympathetic tone, central inhibition of parasympathetic output, peripheral antagonism of opioid peptides released in shock states or a cellular action of stabilization of lysosomes. Certainly, administration of naloxone may be accompanied by a sharp increase in circulating catecholamine concentrations especially in patients with phaeochromocytoma (Manelli et al., 1983). The discovery of opioid peptides in intimate relationship with the splanchnic nerve in the adrenal medulla has led to speculation that these may play a regulatory neurotransmitter role with regard to the release of catecholamines. In addition, a number of opioid peptides have been discovered within the adrenal gland, although their role and significance remain obscure.

Naloxone has been shown to reduce neurological deficit in animals after cerebral and spinal cord ischaemia. Hosobuchi, Baskin and Woo (1981) found that, in gerbils, the clinical signs of stroke produced by carotid occlusion were reversed by intraperitoneal naloxone, although this effect lasted only 30 min. Subsequently, naloxone i.v. was reported to reverse hemiplegia in two patients with stroke, although this effect was again transient. Although one recent report has implicated the vehicle rather than the active drug as the mechanism whereby naloxone exerts its effect in the gerbil model (Crockard et al., 1983), a large body of other experimental data from animal work has confirmed that naloxone may ameliorate the neurological deficit following a cerebral ischaemic insult (see review by Milne and Jhamandas, 1984).

The mechanism of a beneficial effect of naloxone following spinal cord injury defies elucidation, but possible explanations involve an improvement in local blood supply to the ischaemic site, either by a reduction of local oedema or by a direct vascular effect (Faden, 1983).

It seems certain that naloxone can cause an increase in cerebral and spinal cord blood flow, a finding which is consistent with the presence of opioid receptors on CNS vessels. However, there is sufficient conflict in the conclusions drawn from laboratory studies in this area to suggest that considerably more research is required before extrapolations can be made from the experimental to the clinical situation. Data on the clinical use of naloxone in this area are largely anecdotal and the results of controlled studies are required before any recommendations can be made.

Naloxone has been used successfully to treat overdosage with benzodiazepines, alcohol and barbiturates. In the case of alcohol, condensation products resulting from metabolism (the isoquinolines) have opioid-like actions, which may explain this particular antagonist effect. In respect of the benzodiazepines and barbiturates it is possible that a non-specific analeptic action may account for the mechanism of action of naloxone. However, it has been postulated that there is an interaction of the opioid neurotransmitter system with other systems (notably gamma amino butyric acid) and, thus, possibly with the benzodiazepine receptor also, which could provide an alternative explanation.

In addition to these major areas of interest to the anaesthetist, naloxone has also been used in a number of unrelated conditions with apparently beneficial results including: schizophrenia, chronic idiopathic constipation, intractable pruritus and thalamic pain syndrome.

It is clear, therefore, that naloxone cannot be regarded as a simple antagonist of opioid-induced respiratory depression. Whilst many of its diverse and apparently paradoxical actions have now become explicable on the basis of the endogenous opioid peptide system, some await clarification, particularly those actions which are not stereospecific (such as the reversal of the inhibition of spinal neurones caused by GABA).

There is little doubt that the rapid progress currently being made in the elucidation of opioid physiology will provide the basis for understanding many of the complex effects of this agent. The development of receptor-specific antagonists will provide the key to further elucidation of the endogenous opioid system and may also provide the anaesthetist with a drug which will antagonize respiratory depression without the unwanted effects of naloxone, particularly antagonism of analgesia.

G. Smith
C. Pinnock

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ATRACURIUM: CLINICAL STRATEGIES FOR PREVENTING HISTAMINE RELEASE AND ATTENUATING THE HAEMODYNAMIC RESPONSE

R. P. F. SCOTT, J. J. SAVARESE, S. J. BASTA, N. SUNDER, H. H. ALI, M. GARGARIAN, M. GIONFRIDDO AND A. G. BATSON

SUMMARY

This study was designed to determine the effects of a rapid bolus dose of atracurium 0.6 mg kg^{-1} on arterial pressure, heart rate and plasma histamine concentration ($n = 9$), and to compare these values with those obtained by (a) giving the same dose of atracurium slowly (over 75 s) ($n = 9$), or (b) pre-treating with H_1- and H_2- antagonists ($n = 9$). The rapid (5-s) bolus dose of atracurium i.v. resulted in a significant increase in plasma histamine concentration ($P < 0.05$) and was associated with a decrease in mean arterial pressure and an increase in heart rate. Administering the same dose of atracurium slowly (over 75 s) prevented the increase in plasma histamine concentration, and abolished the subsequent haemodynamic response. Pretreatment with cimetidine 4 mg kg^{-1} i.v. and chlorpheniramine 0.1 mg kg^{-1} i.v. abolished the haemodynamic response despite a moderate increase in histamine concentration ($0.1 > P > 0.05$).

All basic compounds may disrupt mast cells and cause the release of histamine if the dose is large enough (Paton, 1957). Among the neuromuscular blocking drugs, this effect appears to be most pronounced with tubocurarine, possibly because of its free hydroxyl groups which are thought to enhance histamine-releasing potency (Buckett and Frisk-Holmberg, 1970). Unfortunately, the lack of a sensitive and reliable assay for plasma histamine has made it difficult to document the role of the histamine so released in drug-induced cardiovascular changes. The recent development of a radioenzymatic technique (Snyder, Baldasserarini and Axelrod, 1966; Beavan, Jacobsen and Horakova, 1972; Beavan and Horakova, 1978; Iverson, Iverson and Snyder, 1979) and its improvement by the discovery of renal histamine-n-methyltransferase (Shaff and Beavan, 1979) have greatly enhanced our ability to detect histamine in clinically important situations.

The histamine-releasing property of tubocurarine occurs within the clinical dose range, and a close correlation between the dose of tubocurarine administered and the amount of histamine released has been documented in man (Moss et al., 1982). In addition, a correlation exists between the plasma histamine concentration and the extent of systemic arterial hypotension. When plasma concentrations are increased by about 200% of control, significant changes are noted in heart rate and arterial pressure (Moss et al., 1982).

More recently, it has been shown that atracurium will also release histamine at the upper end of its clinical dose range (0.6 mg kg^{-1}) and this is associated with corresponding changes in cardiovascular indices (Basta et al., 1983, 1984). The ability of atracurium to release histamine relative to its neuromuscular blocking potency is approximately one-half that of dimethyltubocurarine and less than one-third that of tubocurarine.

A number of clinical strategies have been used to attenuate the adverse reactions to the histamine released by certain drugs. It has been shown that even small time differences in the rate of administration of i.v. agents can lead to significant changes in the likelihood of generating clinically significant histamine release (Rosow et al., 1980; Basta et al., 1981). Furthermore, there is abundant evidence suggesting that the prophylactic use of H_1- and H_2-

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antagonists can also attenuate the haemodynamic responses to certain histamine-releasing drugs, including morphine (Philbin et al., 1981), BW 785U (Rosow et al., 1980), Haemaccel (Lorenz et al., 1980) and tubocurarine (Moss et al., 1982).

This study was designed to determine the effects of a rapid bolus dose of atracurium 0.6 mg kg^{-1} on arterial pressure, heart rate and plasma histamine concentration, and to compare these values with those obtained by (a) giving the same dose of atracurium slowly over 75 s and (b) pretreating with H_1- and H_2-antagonists.

PATIENTS AND METHODS

Twenty-seven (ASA Class I or II) patients gave institutionally approved informed consent to the study, and were assigned to one of three subgroups at the discretion of the investigator. All the patients were aged between 18 and 60 yr, weighed 45–110 kg, and were undergoing elective surgical procedures. Any patient with recent exposure to antihistamines or antidepressants was excluded from the trial.

Premedication consisted of morphine 0.1 mg kg^{-1} i.m. and diazepam 0.2 mg kg^{-1} by mouth. Anaesthesia was induced with fentanyl 3–4 μg kg^{-1} and thiopentone 5 mg kg^{-1} i.v., and maintained with nitrous oxide in oxygen via a face mask. Heart rate (by tachograph), ECG and intra-arterial pressure were recorded continously on a Grass Model 7 polygraph. After a stable 10-min baseline period, a single bolus of atracurium 0.6 mg kg^{-1} was administered over 5 s to patients in group I. Patients in group II received the same dose of atracurium slowly (over 75 s). The patients in group III were pretreated with cimetidine 4 mg kg^{-1} and chlorpheniramine 0.1 mg kg^{-1} i.v. 15 min before induction. They were then given atracurium 0.6 mg kg^{-1} as 5-s bolus. Maximum changes in heart rate and arterial pressure were noted. Intubation of the trachea was delayed for 10 min following the administration of atracurium, to avoid the cardiovascular response to laryngoscopy. Arterial blood samples were drawn immediately before the injection of atracurium and at 2 and 5 min after injection; these samples were analysed for histamine by an isotope radioenzymatic assay technique (Moss et al., 1981). End-tidal carbon dioxide concentration was kept within the normal limits during the course of the study.

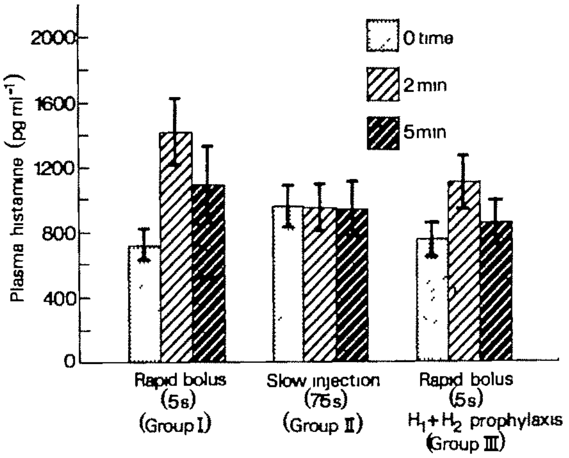

FIG 1. Mean plasma histamine concentrations in the three groups at control, 2 min and 5 min following administration of atracurium 0.6 mg kg^{-1} i.v.

RESULTS

The results are summarized in tables I and II: the data displayed are mean values. The changes in mean arterial pressure and heart rate are the maximum changes that occurred in the 10 min following the administration of atracurium, calculated as a percentage of the baseline values. The absolute values at baseline, 2 min and 5 min for mean arterial pressure and heart rate are displayed in parentheses in table I. Figure 1 illustrates the mean changes in

TABLE I. *Effect of atracurium 0.6 mg kg^{-1} on mean arterial pressure and heart rate. *Actual values at baseline, 2 and 5 min for mean arterial pressure (MAP) (mm Hg) and heart rate (HR) (beat min^{-1}) are shown in parentheses*

	n	MAP (% of baseline)	HR (% of baseline)
Group I: 5-s bolus	9	82.1±6.4 (78.4;63.5;74.8)*	108.6±4.6 (65;70.1;64.1)*
Group II: 75-s dose	9	95.7±2.6 (75.1;71.8,73.5)*	97.7±2.3 (66;64.2;62.4)*
Group III: $H_1 + H_2$ prophylaxis	9	96.2±2.2 (65.7;63.0;65.2)*	102.3±2.2 (60.2;62.1;60.4)*

TABLE II. *Effect of atracurium 0.6 mg kg^{-1} on plasma histamine concentration.* *$P<0.05$ *(one way analysis of variance)*

	Plasma histamine (pg ml^{-1})		
	Control	+2 min	+5 min
Group I 5-s bolus	715.3±93.6	1415.1±203.5*	1086.3±237.9
Group II 75-s slow injection	954.1±131.7	949.9±154.1	939.4±162.7
Group III $H_1 + H_2$ prophylaxis	751.1±113.3	1107.0±160.4	854.1±146.0

plasma histamine concentration in the three groups, and figure 2 the changes in plasma histamine concentration in the individual patients. Patients in group I demonstrated a significant increase in plasma histamine concentration at 2 min ($P < 0.05$; analysis of variance). Seven patients (77%) in this group showed clinical signs of histamine release, with the development of mild to moderate erythema over the trunk and face. The changes in heart rate and arterial pressure in this group were all transient and had almost returned to baseline values by 5 min.

A moderate increase in histamine concentration at the 2-min sample in group III approached, but did not reach, statistical significance ($0.1 > P > 0.05$).

None of the patients in groups II or III showed clinical signs of histamine release nor any haemodynamic changes of statistical or clinical significance.

DISCUSSION

Simple histamine release by many drugs, including neuromuscular blocking agents, does not involve immunological mechanisms but rather a non-specific displacement of histamine and possibly other vasoactive substances from vascular mast cells. The transient nature of the changes in arterial pressure and heart rate following a bolus dose of atracurium 0.6 mg kg^{-1} i.v. and the significant increases in plasma histamine concentration would seem to confirm that this haemodynamic response results from the release of endogenous histamine. Atracurium has a very high margin of safety for ganglionic blockade (Hughes and Chapple, 1981), the duration of which tends to parallel neuromuscular blockade (Savarese, 1976). Thus, a hypotensive response to atracurium mediated via ganglionic blockade would seem unlikely.

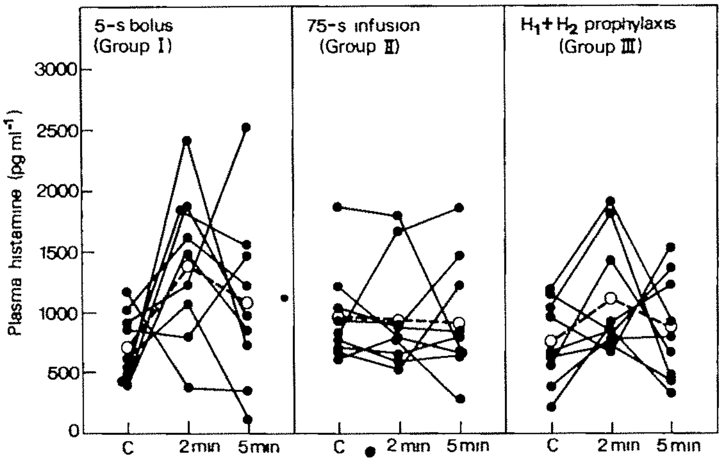

FIG. 2. Plasma histamine concentrations in individual patients in the three groups at control, 2 min and 5 min following administration of atracurium 0.6 mg kg^{-1} i.v.

It appears that small differences in the plasma concentration of a histamine-releasing drug can produce large changes in the amount of histamine liberated. In this study, slowing the administration of atracurium appeared to prevent the increase in histamine concentration and the subsequent change in haemodynamic variables.

The wide variety of agents with which combined histamine–receptor blockade is effective, demonstrates the clinical importance of histamine release as well as the effectiveness of combined blockade. In the present study the patients receiving a rapid bolus of atracurium i.v. who were pretreated with H_1- and H_2-antagonists did show increases in plasma histamine concentration. The haemodynamic response, however, was markedly attenuated.

It should be noted that not all patients will release histamine at high doses of atracurium, as indicated by the large standard error. However, as the size of the bolus dose increases, there is a greater likelihood of this response occurring (Basta et al., 1981). Although this transient haemodynamic response is probably of little clinical significance in the healthy patient, the effect may be more important in the haemodynamically unstable patient who is hypovolaemic, or has cardiovascular disease.

We conclude that the release of histamine by large bolus doses of atracurium (0.6 mg kg^{-1}), and any associated haemodynamic response, can be prevented by administering the dose slowly (over 75 s). In addition, the haemodynamic response to a rapid (5-s) bolus can be minimized by pretreatment with H_1- and H_2-receptor antagonists such as chlorpheniramine and cimetidine i.v., given 15 min before the atracurium.

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EFFECT OF ETOMIDATE ON THE AUDITORY EVOKED RESPONSE IN MAN

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SUMMARY

The effect of etomidate on the auditory evoked response was examined in a double-blind study carried out before the start of surgery. Fourteen patients were anaesthetized with 70% nitrous oxide and oxygen after induction with thiopentone. Ventilation was controlled. Seven of the patients received a continuous infusion of etomidate, increasing in five equal steps from 0.01 mg kg^{-1} min^{-1} to 0.05 mg kg^{-1} min^{-1} over a period of 50 min. The other seven received similarly an equivalent volume of saline. The patients given etomidate were easily distinguishable from those given saline, solely on the basis of changes in the early cortical peaks Pa and Nb. In the etomidate group the latencies of these peaks increased and their amplitudes decreased. These changes were linearly related to serum etomidate concentration. There was no effect of etomidate on the brainstem response.

The traditional signs of general anaesthesia are obscured or absent when neuromuscular blocking drugs have been administered, and during total i.v. anaesthesia with the newer anaesthetic agents. A reliable technique to assess the depth of anaesthesia would be of great value under such circumstances and, if the technique could be used with all general anaesthetic agents, the anaesthetist could control the dose of anaesthetic agent more precisely and decrease the likelihood of awareness. The ideal technique would display a signal proportional to the depth of anaesthesia, show dose-related changes with all general anaesthetic agents, and be unaffected by neuromuscular blockade.

We have reported previously (Thornton et al., 1984) that components of the auditory evoked response show dose-related changes with the inhalation agents halothane and enflurane. These components, waves III, V, Pa and Nb, represent neural activity in the brain stem and primary cortical sections of the auditory pathway which has been initiated by a sound stimulus. They are not affected by myoneural blocking drugs.

If similar changes occur with other anaesthetic agents, it may be possible to use the auditory evoked response to assess depth of anaesthesia. In this paper we have examined the effects of the administration of etomidate i.v. The aims were to determine, first, whether etomidate had an effect on the auditory evoked response and, second, if this effect was dose-related. The entire study was carried out before surgery as we wished to avoid any possible effects of surgical stimulation on the response.

PATIENTS AND METHODS

Patients

Fourteen patients, aged 18–45 yr gave informed consent to an experimental programme approved by Harrow District Ethical Committee. The first 12 patients were randomly allocated in a double-blind manner to two groups. Five patients, the etomidate group, received an infusion of etomidate and the other seven, the saline group, received an equivalent volume of saline. Subsequently, a further two patients were added to the etomidate group to equalize the numbers.

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Anaesthesia

After premedication with morphine 10 mg and atropine 600 μg, anaesthesia was induced with thiopentone 2–4 mg kg^{-1} i.v. The trachea was intubated after the administration of pancuronium 0.1 mg kg^{-1} and the lungs were ventilated with 70% nitrous oxide in oxygen. An infusion i.v. of either etomidate* or saline was started 7 min after induction. In the etomidate group, the infusion was started with etomidate 0.01 mg kg^{-1} min^{-1} and increased in four equal increments to 0.05 mg kg^{-1} min^{-1}. Each infusion rate was maintained for 10 min. In the saline group, equivalent volumes of saline were infused over the same time period. In one patient in the etomidate group, the start of surgery was delayed, and so the infusion was discontinued, while artificial ventilation was maintained (with 70% nitrous oxide in oxygen).

Throughout the infusion and recovery periods, end-tidal carbon dioxide concentration (Godart 17070 infra-red analyser corrected for the effects of nitrous oxide) was kept constant to within 0.2 kPa of the starting value (range 4.5–5.5 kPa) by adjusting the minute volume. Body temperature was monitored using a thermistor in the oesophagus at the level of the aortic arch. Arterial pressure and heart rate were recorded at 5–10-min intervals.

Recording the auditory evoked response

The detailed technique has been described previously (Thornton et al., 1983). In outline, binaural clicks of 75 dB intensity and 0.5 ms duration were presented through headphones at a rate of 6 per second. The EEG was recorded from silver–silver chloride disc electrodes at mastoid, inion and vertex with an FM tape recorder (RACAL 4).

The tapes were replayed through a DATALAB DL4000 to produce an average of the EEG for the 80 ms following 2048 clicks. This average, the auditory evoked response, took 5.7 min to record. Evoked responses were obtained before the induction of anaesthesia, and during the last part of the induction period and of each infusion period. In the patient in whom the infusion was discontinued after the highest concentration had been administered, averaged responses (following 1024 clicks) were taken throughout the recovery period. The latency and amplitude of waves I, III, V, Pa and Nb of each average were measured.

Measurement of anaesthetic concentration

Venous blood samples were drawn from the arm opposite to that receiving the infusion at the end of the induction period, and in the 5th and 10th min of each infusion period. In the one patient whose recovery was monitored, a sample was taken at the end of this period.

Extraction of etomidate from serum for high pressure liquid chromatography (HPLC) was by a method described by Ellis and Beck (1982) using propoxate as internal standard. Samples were analysed subsequently by injecting 100 μl of extract to a 5-μm ODS-Hypersil column (25 cm × 4.6 mm i.d.) with a mobile phase of 40% acetonitrile (HPLC Grade) and 60% ammonium acetate 0.2 mol $litre^{-1}$ at a flow of 1 ml min^{-1}. Detection was at 248 nm: lower limit of detection 0.01 μg/ml serum.

Analysis of data

The electrophysiologist examined the traces for each patient in the blind study. Depending on whether or not there were consistent changes, patients were allocated to either "etomidate" or "saline" groups.

After the code had been broken, the data of the two extra etomidate patients were added to the etomidate group. Variables examined were the latencies and amplitudes of waves I, III, V, Pa, Nb and the interpeak intervals I-III, I–V, III–V. Satistical analyses were carried out to test for effects of etomidate on the auditory evoked response, and dose relationships of these effects.

To test for effects on the auditory evoked response. The etomidate and saline groups were compared by plotting each of the above variables for individual patients against time from the start of the first infusion. Parallel regression lines for each of the seven patients in the etomidate group were fitted using a computer program (MINITAB) (Ryan, Joiner and Ryan, 1976). This assumes that variations in the slopes between the patients in the group were random. The same procedure was carried out for the saline group. The etomidate and saline slopes were compared using a *t* test to demonstrate any significant differences.

To see whether the effects were dose-related. The changes in the above variables with changing serum etomidate concentration were examined. As the averaged responses were recorded over the second half of each 10-min period, the mean of the serum concentration in the blood samples drawn in the 5th and 10th min was used as a basis for comparison.

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*At the time of this study, etomidate was still available for use by continuous infusion.

Each variable was plotted against serum concentration for each patient in the etomidate group. A regression line representing the group was calculated and the significance of the slope was tested.

RESULTS

Double-blind study: early cortical response

When the code for the double-blind study was broken, it was found that the electrophysiologist had correctly identified all patients in the etomidate group. The difference between the two groups was easily seen and was confined to the early cortical response.

The effect of etomidate. Typical examples of the early cortical responses of two patients, one who received saline, and the other who received etomidate are shown in figure 1. There was an increase in latency, and decreases in the amplitude of waves Pa and Nb in the patient who received etomidate whereas no such changes were evident in the patient who received saline.

Statistical analyses of the data for the whole group confirmed these effects. The slopes of Pa and Nb latency and amplitude *v.* time in the etomidate group were significantly different from the corresponding slopes in the saline group (table I).

Dose relationship of the effect. The changes in latency and amplitude in the etomidate patients were progressive with increasing serum concentration (fig. 1). Pa latency increased from 26 to 35 ms and Nb latency from 32 to 67 ms as the etomidate concentration was increased from 0.01 to 0.53 μg ml^{-1}. Once again, statistical analysis of the group data confirmed this relationship, in that the slopes relating Pa and Nb latency and amplitude to serum concentration were significant (table II). The changes in latency and amplitude of Pa and Nb were related to the serum concentration of etomidate and not to time. This is illustrated in figure 2, in which the patient whose evoked responses are shown on the left had a serum concentration of 0.26 μg ml^{-1} after 50 min, and the changes in Pa and Nb were very similar to those shown on the right, where the serum etomidate concentration was 0.29 μg ml^{-1} at only 20 min. The final serum etomidate concentration ranged from 0.32 to 1.72 μg ml^{-1} for the group, despite the same infusion rates (fig. 3). In one patient (P7), etomidate was not detected in serum until the fourth infusion rate had been started.

In this same patient, the infusion was discontinued once the highest concentration had been administered. The latencies continued to increase and the amplitude to decrease for 3 min, then the changes in the early cortical response began to reverse so that, 10 min after the discontinuation of the infusion, the early cortical response was almost identical in appearance to the post-induction recording. By this time the serum etomidate concentration had decreased to 0.06 μg ml^{-1} (fig. 4).

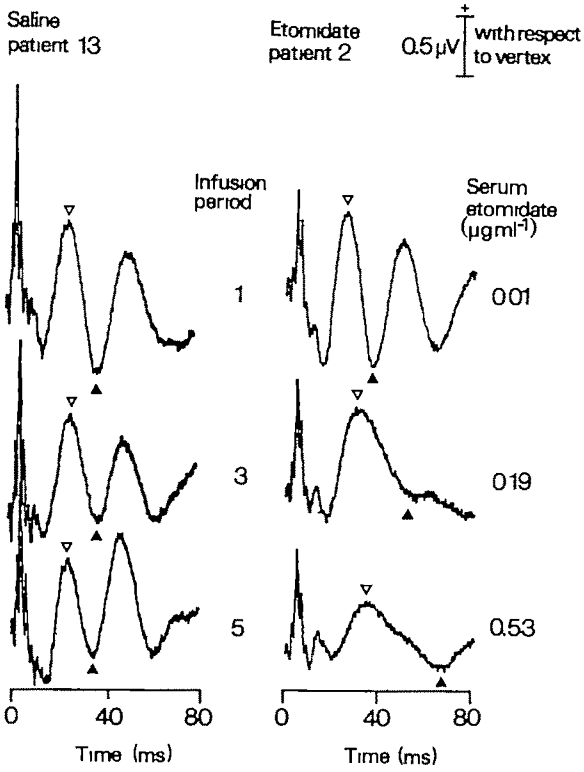

FIG. 1. Averaged early cortical evoked responses of two patients, one who received a saline infusion (left) and the other who received saline with etomidate added (right). The traces represent the first, third and fifth infusion periods. The serum etomidate concentrations corresponding to these rates are given. Pa (▽) and Nb (▲) occur at approximately 26 and 37 ms in conscious patients.

Brainstem response

The effect of etomidate. The brainstem responses of the patients in the etomidate group were indistinguishable from those in the saline group. Figure 5 gives typical examples of the brainstem responses of two patients, one who received saline, the other who received etomidate. There is no essential difference between the two traces. Neither of these patients showed changes in the latency or amplitude of I, III or V.

TABLE I. *Regression analyses of latency (ms) and amplitude (μV) against time (min) for the etomidate and saline groups. Common slopes, their standard errors (each with 27 degrees of freedom), the difference between the slopes and the significance* (P) *of the difference of the slopes*

	Etomidate		Saline		Etomidate–saline diff.	
	Slope × 10^{-2}	SE Slope × 10^{-2}	Slope × 10^{-2}	SE Slope × 10^{-2}	Diff. between Slopes × 10^{-2}	*P*
Early cortical						
Latency (ms min^{-1})						
Pa	49.8	8.65	−1.2	2.67	51.0	<0.001
Nb	65.3	12.0	−2.0	4.80	67.3	<0.001
Amplitude (μV min^{-1})						
Pa	−1.25	0.292	−0.51	0.173	−0.74	<0.05
Nb	−1.26	0.285	−0.52	0.201	−0.74	<0.05
Brainstem						
Latency (ms min^{-1})						
I	0.14	0.096	0.25	0.073	−0.11	ns
III	0.10	0.042	0.06	0.049	0.04	ns
V	0.11	0.039	0.18	0.072	−0.07	ns
I−III	−0.04	0.110	−0.19	0.095	0.15	ns
I−V	−0.02	0.099	−0.07	0.090	0.07	ns
III−V	0.02	0.062	0.12	0.077	−0.10	ns
Amplitude (μV min^{-1})						
III	0.06	0.020	0.00	0.030	0.06	ns
V	0.02	0.029	−0.02	0.037	0.04	ns

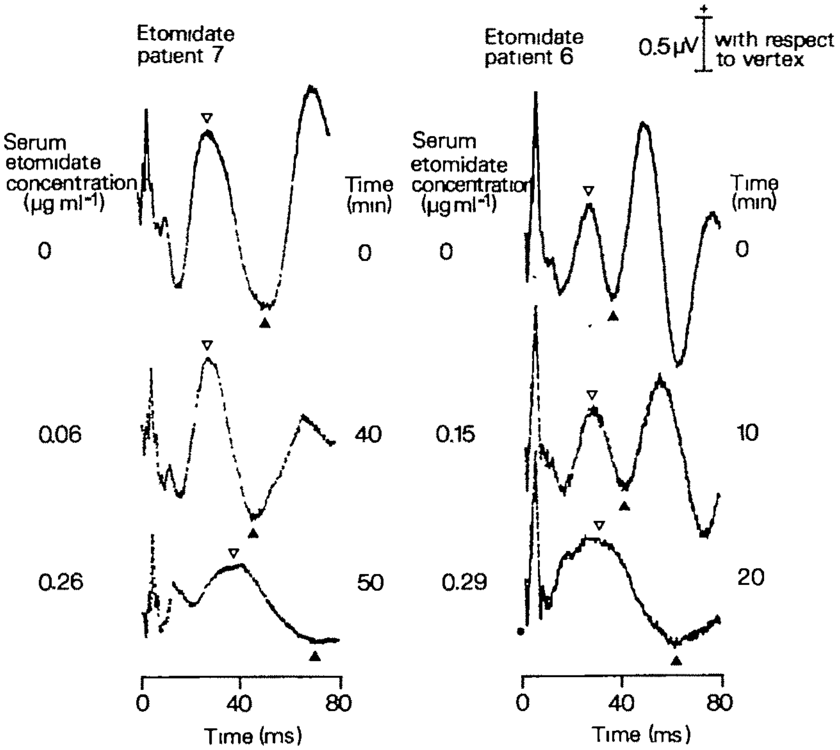

FIG 2. Averaged early cortical response of two patients following induction of anaesthesia and at the serum concentrations and times shown.

TABLE II. *Regression analyses of latency (ms) and amplitude (μV) against serum concentration of etomidate ($\mu g\ ml^{-1}$) for the etomidate group. Common slope, their standard errors and the significance* (P) *of the slopes* (n = 7)

	Slope	SE Slope	*P* of Slope
Early cortical			
Latency ($ms\ \mu g^{-1}\ ml^{-1}$)			
Pa	22.6	3.12	<0.001
Nb	28.3	4.72	<0.001
Amplitude ($\mu V\ \mu g^{-1}\ ml^{-1}$)			
Pa	−0.50	0.124	<0.05
Nb	−0.49	0.124	<0.001
Brainstem			
Latency ($ms\ \mu g^{-1}\ ml^{-1}$)			
I	0.04	0.040	ns
III	0.04	0.017	<0.05
V	0.02	0.018	ns
I–III	0.00	0.046	ns
I–V	−0.02	0.041	ns
III–V	−0.02	0.026	ns
Amplitude ($\mu V\ \mu g^{-1}\ ml^{-1}$)			
III	0.02	0.009	<0.05
V	0.00	0.012	ns

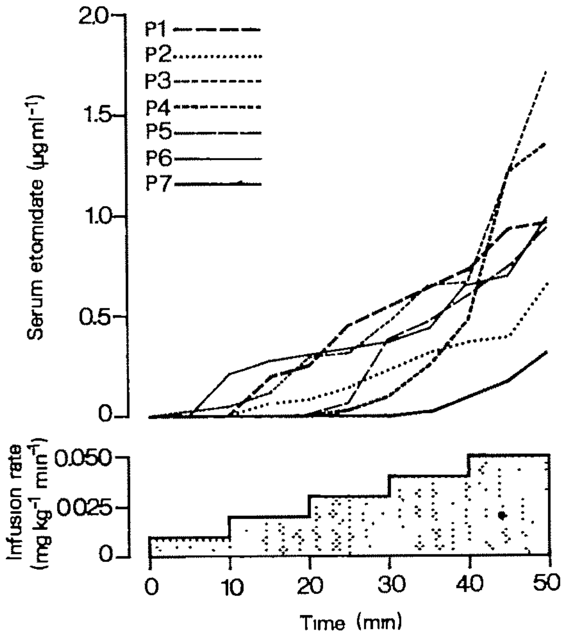

FIG. 3. The relationships between infusion time (min) and serum concentration of etomidate in seven patients who received etomidate.

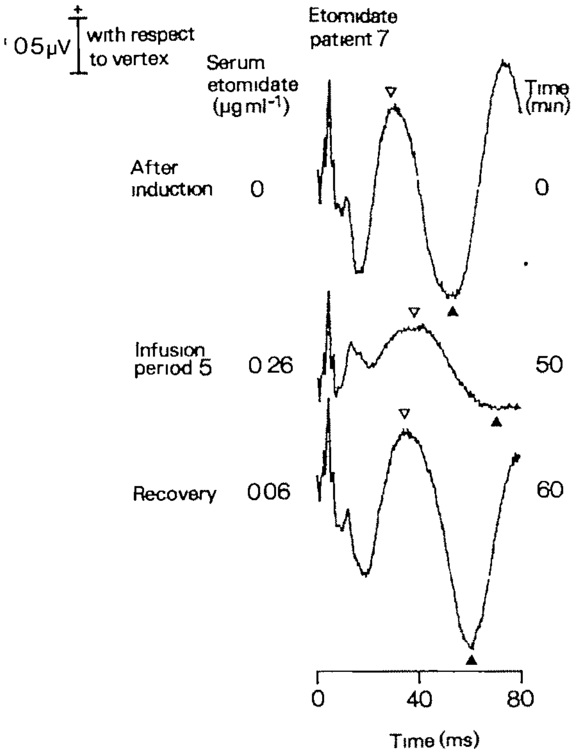

FIG 4. Averaged early cortical response for the patient in whom the etomidate infusion was discontinued after the fifth infusion period. The traces were obtained after induction of anaesthesia; at the time of the highest serum concentration of etomidate achieved in this patient (0.25 $\mu g\ ml^{-1}$); and 10 min later, when the serum etomidate concentration had decreased to 0.06 $\mu g\ ml^{-1}$. ▽ = Pa; ▲ = Nb.

The slopes of the latencies and amplitudes of I, III and V and interpeak intervals I–III, I–V, III–V, *v.* time were not significantly different from the corresponding slopes in the saline group (table I).

Dose relationship of the effect. The slopes of these variables against serum etomidate concentration were not significant, with the exceptions of the latency and amplitude of wave III, both of which increased with increasing concentration (table II).

Body temperature, end-tidal carbon dioxide concentration and arterial pressure

There were no major changes in any of these variables. Table III gives the mean and SEM of the changes in end-tidal carbon dioxide concentration, arterial pressure and oesophageal temperature over the whole infusion period. Small decreases in body temperature (max 0.5 °C) did occur in some, but not

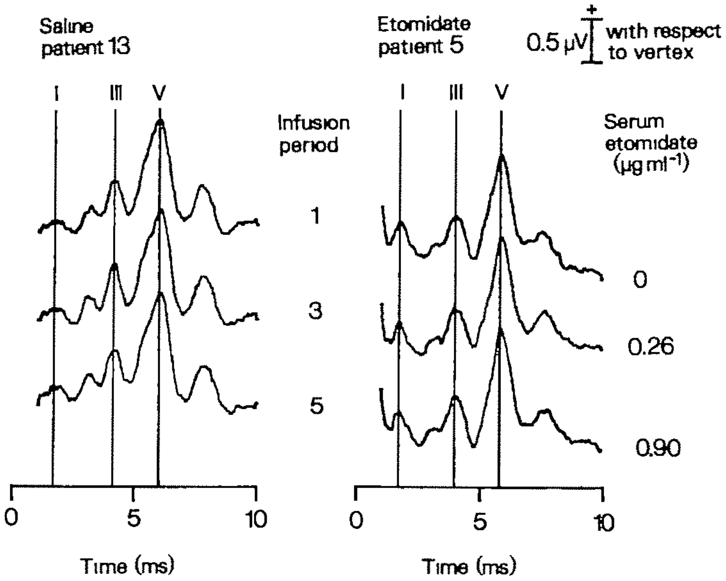

FIG 5. Averaged brainstem evoked responses of two subjects, one who received a saline infusion (left) and the other who received saline with etomidate added (right). The traces represent the first, third and fifth infusion periods. The serum etomidate concentrations corresponding to these rates are given. Vertical lines are drawn through waves I, III and V.

TABLE III. *Changes in end-tidal carbon dioxide concentration (kPa), systolic arterial pressure (mm Hg) and oesophageal temperature (°C) for the test and control groups over the 50-min period of the infusion. Significance* (P) *of differences between the two groups* (t *test) is also given*

	Saline ($n = 7$) Mean (SEM)	Etomidate ($n = 7$) Mean (SEM)	P
ΔEnd-tidal CO_2 (kPa)	−0.17 (0.07)	−0.10(0.07)	ns
ΔSystolic AP (mm Hg)	3 (3)	−10 (5)	=0.05
ΔOesophageal temp. (°C)	−0.2 (0.05)	−0.2 (0.10)	ns

all, subjects. In both groups there were minimal changes in the end-tidal carbon dioxide concentration. Arterial pressure never decreased to less than 80 mm Hg systolic, although the mean decrease of 10 mm Hg in the test group was just significantly different ($P = 0.05$) from the mean increase which occurred in the control group. This mean change in the test group was also significantly different ($P = 0.05$) from those changes seen with halothane and enflurane in our previously reported study: −28 (5) mm Hg and −28 (3) mm Hg (mean (SEM)) respectively.

DISCUSSION

All patients who received etomidate, even when the drug status of the patients was not known, were easily distinguishable from controls solely on the basis of changes in the early cortical part of the auditory evoked response. Furthermore, the changes in the early cortical response were dose-related, in that the latency of Pa and Nb increased and their amplitude decreased linearly with increasing concentration. The effects on wave amplitude and latency were related to drug concentration and not to time because: (1) the changes were not seen in the saline group, which had the same schedule but no etomidate; (2) the changes were similar in patients with similar serum concentrations at different times; (3) the changes in Pa and Nb returned almost to pre-infusion values when the infusion was discontinued following the highest concentration. At this time, 1 h following the start of the infusion, the serum concentration was virtually zero.

Etomidate produced changes in the early cortical response which were similar to those observed with the inhalation agents halothane and enflurane (Thornton et al., 1984) (fig. 6). With these agents, the effects were also dose-related. Furthermore, all three agents produced changes of a similar magnitude over an approximately equipotent range etomidate (0–0.66 µg ml⁻¹ equates with 0–1.3%

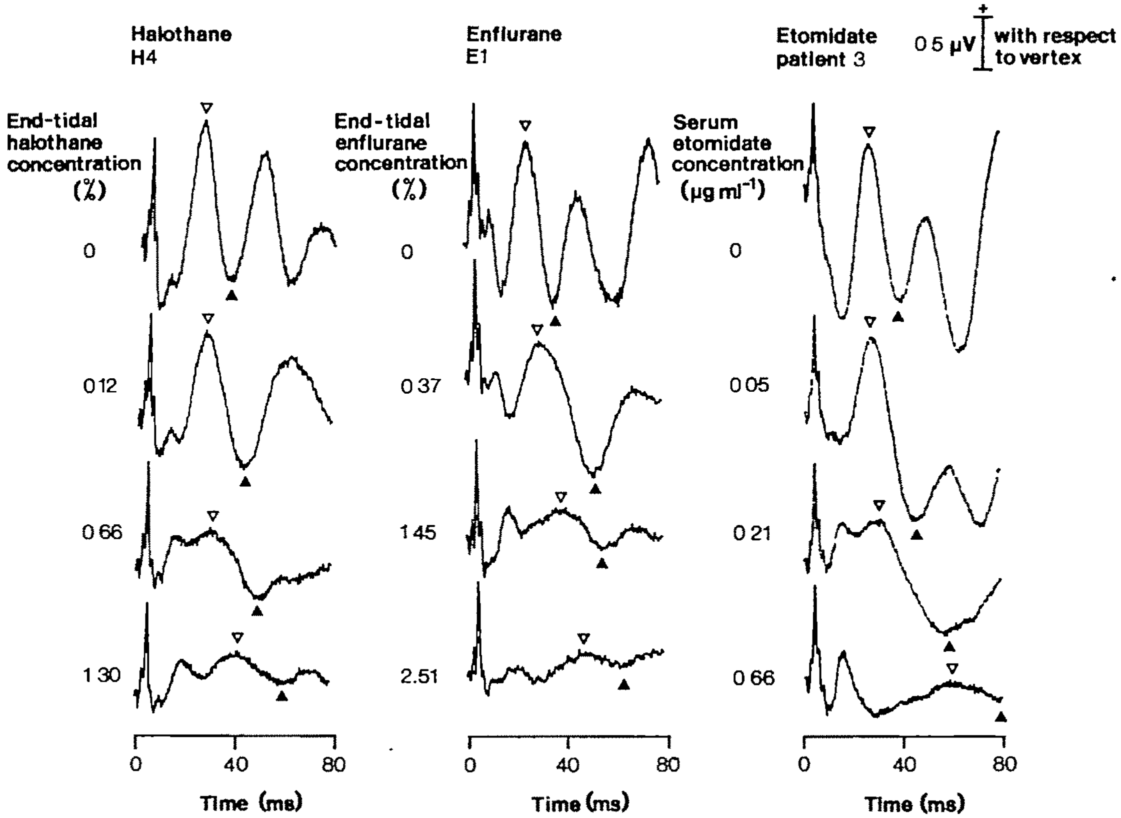

FIG 6 Averaged early cortical evoked responses of three patients, one who received halothane (left) one who received enflurane (centre) and one who received etomidate (right). The traces were obtained after induction of anaesthesia and at the concentrations given Halothane 0–1.3%, 0–2.5% enflurane and etomidate 0–0.66 $\mu g\ ml^{-1}$ are approximately equipotent (see text). ▽ = Pa; ▲ = Nb.

halothane or 0–2.5% enflurane). (The plasma concentration of etomidate when patients are just rousable is 0.14–0.2 $\mu g\ ml^{-1}$ (Doenicke et al., 1982; Schüttler, Schurlden and Stoekel, 1983). If this is in the same ratio to the anaesthetizing concentration as "MAC awake" is to "MAC" for inhalation agents, that is 0.6 (Stoelting, Longnecker and Eger, 1970), then we can calculate an "MAC equivalent" of etomidate of 0.2–0.3 μg/ml plasma concentration; "MAC" for halothane is 0.75; "MAC" for enflurane is 1.68 (Eger, 1974).)

The etomidate and saline groups could not be distinguished on the basis of any of the brainstem variables and we conclude that etomidate does not affect the brainstem response. Although there was no difference between the etomidate and saline groups when the latency and amplitude of wave III were plotted against time, these variables showed significant increases with etomidate concentration. These changes were small in magnitude (table II). Furthermore, the slope of the interpeak interval from I to III against serum concentration had a value of 0.00 ms $\mu g^{-1}\ ml^{-1}$, suggesting that the increase in the latency of wave III may have been the result of an increase in the latency of wave I. We would have expected the amplitude of wave III to decrease, if anything, with increasing etomidate concentration and, therefore, tend to dismiss these changes in wave III as chance findings.

Etomidate differs from halothane and enflurane in that the inhalation agents produced marked dose-related increases in the latencies of III and V and in the interpeak interval from III to V (Thornton et al., 1984). It is interesting that these agents produce a profound depression of respiration and circulation which etomidate does not (Kugler, Doenicke and Laub, 1977). The severity of the side effects of the inhalation agents probably results in part from the depression of brainstem structures, and it is possible that this is related to their effects on the brainstem components of the auditory evoked response.

The fact that anaesthesia with etomidate can be produced without an effect on a major part of the brainstem is an important observation. The idea that the state of anaesthesia results from a global action on the brain has been proposed (Halsey, 1974) and the reticular activating system is thought to be a particularly important site of anaesthetic action. The suggestion is that a decrease in activity in the brainstem causes a block in transmission to higher levels. However, it is clear from our results that, in the case of the auditory pathway at least, an anaesthetic can affect the cortex directly without producing a demonstrable effect on brainstem structures. This confirms our previous impression that changes in the brainstem and early cortical waves were not necessarily causally related. After withdrawal of halothane we saw almost complete recovery of Pa and Nb at a time when III and V had not recovered at all (Thornton et al., 1984). Among the possible interpretations of this observation was that the subtle changes in the brainstem components were not the cause of the major changes in the early cortical part of the auditory evoked response. The lack of effect of etomidate on the brainstem waves supports this hypothesis, and the idea that the state of anaesthesia results from actions at a cortical level. This being the case, the effects of anaesthetics on the brainstem components can probably be regarded as side effects.

The final serum concentration varied considerably between patients, in spite of their receiving the same amount of etomidate on a weight basis (1.5 mg kg^{-1}) over the 50-min infusion period. In one patient, etomidate was not detectable until after 35 min of infusion and the final serum concentration in this patient was 0.32 μg ml^{-1}. At the other extreme, in another patient, the final concentration was 1.72 μg ml^{-1}. This pronounced variability emphasizes the need for a feedback system for administering i.v. agents.

In conclusion, the waves Pa and Nb of the early cortical response showed dose-related changes with etomidate similar to those seen with halothane and enflurane and the magnitude of these changes was roughly in keeping with their anaesthetic potency. The brainstem response was unaffected by etomidate. The difference between etomidate and the inhalation agents in this respect is interesting in relation to the possible sites of action of these agents. It also means that the brainstem response would be unsuitable as a universal method for measuring depth of anaesthesia. For this purpose, we should concentrate on the early cortical section of the auditory evoked response.

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VENTILATORY RESPONSES OF CHILDREN TO CHANGES IN DEADSPACE VOLUME

Studies Using the T-Piece (Mapleson F) System

A. J. CHARLTON, S. G. E. LINDAHL AND D. J. HATCH

SUMMARY

Twelve patients (4.3–25.3 kg) undergoing minor surgical procedures were investigated during halothane anaesthesia with spontaneous breathing through a modified T*-piece (Mapleson F) with an apparatus deadspace that could be changed from 2 ml (V_D^{small}) to 16 ml (V_D^{large}). Immediately following the switch from V_D^{small} to V^{large} E_{TCO_2} (mean ± 1 SD) increased from 6.89 ± 1.09% to 7.61 ± 1.14% (ns) then gradually decreased during a 10-min period. The initial plateau of F_{ICO_2} (mean ± 1 SD) with V_D^{large} was 0.74 ± 0.34%, but gradually decreased to 0.63 ± 0.25% after 10 min. This was achieved by an increase in $\dot{V}_E$ ($P < 0.05$ by 2 min). After 10 min $\dot{V}_E$ had increased by more than 40% ($P < 0.01$) as a result of an increase in V_T (mean ± 1 SD) of 14.6 ± 6.5 ml. After 10 min of V_D^{large} ventilation, $\dot{V}_A$ and $\dot{V}_{CO_2}$ were maintained at V_D^{small} values. The adequate ventilatory response to the large deadspace was seen in all patients, but the ventilatory efficiency, as judged by* V_D/V_T *and* $\dot{V}_E/\dot{V}_{CO_2}$ *ratios, was reduced significantly in the children weighing less than 10 kg.*

Alveolar deadspace is greater during anaesthesia than in the conscious state (Nunn and Hill, 1960), and during spontaneous ventilation it increases with depth of anaesthesia (Kain, Panday and Nunn, 1969). However, although the additional influence of apparatus deadspace was investigated by Kain, Panday and Nunn (1969), few studies have considered the effects of apparatus deadspace on anaesthetized children, although these are relatively more important in smaller patients. In one study in children anaesthetized with halothane (Lindahl, Hulse and Hatch, 1984), smaller children were shown to have a higher percentage deadspace ventilation as a result of their higher respiratory rates and of a higher total deadspace to tidal volume ratio, while net deadspace (apparatus deadspace excluded) to tidal volume ratio did not differ with rate.

In this study, the ventilatory responses to two different apparatus deadspaces (2 and 16 ml) were compared in spontaneously breathing children during halothane anaesthesia, and the efficiency of ventilation in younger and older children evaluated.

PATIENTS AND METHODS

Twelve patients, aged between 3 weeks and 6 yr, and weighing between 4.3 and 25.3 kg (mean ± SD: 11 kg ± 5.6) were studied. All were in-patients, free from cardiorespiratory disease, undergoing a variety of minor surgical procedures such as lens aspiration, corrections of hypospadias, repair of cleft palate and orchidopexy. Seven children younger than 1 year of age and weighing less that 10 kg (mean ± SD: 7.6 ± 2.1 kg) received atropine 0.2–0.4 mg i.m. for premedication. Of the other five patients (weight > 10 kg; mean ± SD: 15.8 ± 6.2 kg), three weighing between 10 and 15 kg were premedicated with pethidine compound 0.07 ml kg^{-1} and atropine 0.2–0.4 mg i.m. about 1.5 h before the operation. (Pethidine compound 1 ml contains pethidine 25 mg, chlorpromazine 6.25 mg and promethazine 6.25 mg.) The other two patients (> 15 kg) received papaveretum 0.4 mg kg^{-1} and hyoscine 0.008 mg kg^{-1} i.m. 1.5 h before surgery.

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Anaesthesia

Anaesthesia was induced with cyclopropane in oxygen ($F\text{I}_{\text{O}_2}$ 0.5). The trachea was intubated in all patients after the injection of suxamethonium 1–1.5 mg kg^{-1} i.v. Ventilation was spontaneous throughout, and anaesthesia was maintained with nitrous oxide and 0.5–2% halothane in oxygen ($F\text{I}_{\text{O}_2}$ 0.5). In two patients undergoing the correction of hypospadias, a caudal block was established after induction using 0.25% bupivacaine 0.5 ml kg^{-1}.

The anaesthetic system was a modified T-piece (Mapleson F system) (fig. 1). To avoid rebreathing, the fresh gas flow was set according to the formula: FGF = 3(1000 + 100 kg) (Froese and Rose, 1982). The patient limb of the small deadspace system had a volume of 2 ml ($V\text{D}^{\text{small}}$) consisting of the airway adaptor to a Hewlett–Packard in-line capnograph (14360 A) and a modified Y-piece.

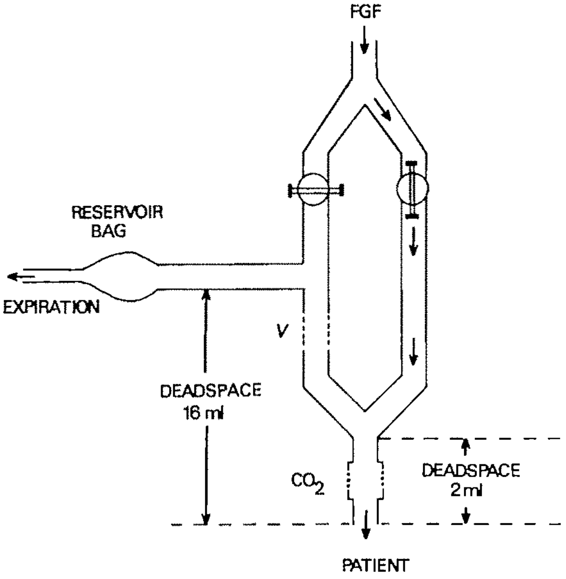

FIG. 1. Presentation of the two systems used. Fresh gas flow (FGF) was directed to the small (2 ml) or to the large (16 ml) deadspace systems by the use of two valves. The figure illustrates the use of small deadspace. CO_2 denotes the position of the in-line capnograph and *V* the position of the pneumotachograph.

The patient limb of the large deadspace system had a volume of 16 ml ($V\text{D}^{\text{large}}$) as a result of the addition of a Fleisch No. 0 pneumotachograph and a T-piece connection. Minute ventilation ($\dot{V}\text{E}$) was derived by electrical integration of the flow signal from a differential pressure manometer (Validyne MP 45-1-871, range ± 2 cm H_2O). Flow volume and carbon dioxide signals were recorded by a u.v. recorder (S.E. Labs (EMI) Ltd, S.E. 3006). Volume was calibrated with a 50-ml syringe, and the capnograph by using certified gas mixtures containing oxygen–nitrogen–carbon dioxide within the measuring range. All carbon dioxide values were corrected by a factor of 0.95 because of the collision broadening effect of nitrous oxide (Kennel, Andrews and Wollman, 1973). The resistance at 7 litre min^{-1} was 3.5 cm H_2O litre^{-1} s^{-1} in the $V\text{D}^{\text{small}}$ system and 7.0 cm H_2O litre^{-1} s^{-1} in the $V\text{D}^{\text{large}}$ system.

Measurements

No measurements were made until at least 20 min after the induction of anaesthesia. During breathing through the $V\text{D}^{\text{small}}$ system, end-tidal carbon dioxide (ET_{CO_2}) was measured and a 3–5-min collection of expired gas made through a dry gas meter (AB Nordgas, Stockholm, Sweden) into a Douglas bag for determination of expired carbon dioxide fraction ($F\bar{\text{E}}_{\text{CO}_2}$). The fresh gas flow (FGF) was then redirected through the $V\text{D}^{\text{large}}$ system. Tidal volume ($V\text{T}$), respiratory rate (*f*), ET_{CO_2}, and inspired carbon dioxide concentration measured from the plateau phase (plateau $F\text{I}_{\text{CO}_2}$) (fig. 3), were measured immediately (i.e. breaths 5–10, time 0) and then every minute for up to 5 min, following which a timed collection (3–5 min) of expiratory gas was obtained. FGF was then redirected to the $V\text{D}^{\text{small}}$ and ET_{CO_2} recorded. After 5 min a further timed collection of expiratory gas was obtained.

Calculations

$\dot{V}\text{E}$, $\dot{V}\text{A}$, $V\text{T}$, deadspace volume ($V\text{D}$), deadspace ventilation ($\dot{V}\text{D}$) and carbon dioxide output ($\dot{V}\text{CO}_2$) are presented at body temperature and pressure saturated (BTPS).

The following formulae were used:

$$\dot{V}\text{CO}_2\ (\text{ml min}^{-1}) = \frac{\text{gas collection } \dot{V}\text{E} \cdot F\bar{\text{E}}_{\text{CO}_2}}{100}$$

$$\dot{V}\text{A}\ (\text{ml min}^{-1}) = \frac{\dot{V}\text{CO}_2 \cdot 100}{\text{ET}_{\text{CO}_2}}$$

$$\dot{V}\text{D}\ (\text{ml min}^{-1}) = \dot{V}\text{E} - \dot{V}\text{A}$$

$$V\text{D}\ (\text{ml}) = \frac{\dot{V}\text{D}}{f}$$

Statistics

Mean values and standard deviation (SD) were calculated. The results were evaluated by the use of paired Student's *t* test.

RESULTS

During measurements, using the small and large deadspaces, mean values (± 1 SD) of systolic and diastolic arterial pressure and heart rate were virtually unchanged (table I).

Minute ventilation, tidal volume and respiratory rate

Within a few breaths of large deadspace ventilation, minute ventilation increased. Measurements showed, for the first 5–10 breaths, a minute ventilation (mean ± 1 SD) of 1594 ± 430 ml min^{-1}, at 1 min 1900 ± 536 ml min^{-1} (ns) and at 2 min 2068 ± 520 ml min^{-1} ($P < 0.05$) (fig. 4). After 10 min, $\dot{V}_E$ had increased by more than 40% to 2303 ± 792 ml min^{-1} ($P < 0.01$). Respiratory rates were unchanged throughout the 10 min of V_D^{large} ventilation and the ventilatory response was the result of larger tidal volumes (fig. 4). During the first 5–10 breaths, V_T was 44 ± 22 ml and increased by 16% to 51 ± 23 ml (ns) 1 min later. After 2 min, V_T increased further, to 55 ± 24 ml (ns), and after 10 min it was 59 ± 26 ml (ns). The overall mean increase of V_T (± 1 SD) was 14.6 ± 6.5 ml.

TABLE I. *Mean values (± SEM) in all 12 patients for arterial pressure (AP) and heart rate (HR) with small (V_D^{small}) and large (V_D^{large}) deadspace ventilation*

	V_D^{small}	V_D^{large}						
	−1	0	1	2	3	4	5	10
AP (mm Hg)								
Systolic	98±4	95±6	97±5	94±5	97±5	97±5	96±5	95±5
Diastolic	50±4	50±5	49±4	50±5	50±4	48±3	48±4	51±4
HR (beat min^{-1})	143±10	142±11	142±11	142±11	141±11	141±11	140±10	140±10

	V_D^{small}						
	0	+1	+2	+3	+4	+5	+10
AP (mm Hg)							
Systolic	95±5	98±5	96±5	97±6	96±5	96±4	99±5
Diastolic	55±6	52±5	50±5	50±5	51±4	52±4	50±5
HR (beat min^{-1})	139±11	136±10	136±10	135±10	136±10	136±10	131±10

End-tidal and inspired CO_2 concentration

With the small deadspace, the mean value (± 1 SD) of $E_{T_{CO_2}}$ concentration was 6.89 ± 1.09%. Immediately on changing to the large deadspace, $E_{T_{CO_2}}$ increased to a mean value (± 1 SD) of 7.61 ± 1.14%. During the period of observation, $E_{T_{CO_2}}$ gradually decreased to a mean value of 7.0 ± 1.30% after 10 min (fig. 2). One minute after changing to the small deadspace again, $E_{T_{CO_2}}$ decreased to a mean (± 1 SD) of 6.50 ± 1.35% (fig. 2) and continued to decrease over 5 min to 6.33 ± 1.36%. At 10 min $E_{T_{CO_2}}$ had stabilized at a mean value (± 1 SD) of 6.50 ± 1.34%.

Mean value (± 1 SD) of inspired carbon dioxide plateau (plateau $F_{I_{CO_2}}$) was also greatest (0.74 ± 0.34%) immediately after changing to the large deadspace. It decreased to 0.65 ± 0.23% at 5 min and was 0.63 ± 0.25% after 10 min (fig. 2). The mean values (± 1 SD) of the end-tidal and inspired carbon dioxide concentrations and a typical carbon dioxide curve, are demonstrated in figure 3.

Alveolar ventilation and carbon dioxide elimination

During V_D^{small} ventilation, the alveolar ventilation (mean ± 1 SD) was 929 ± 343 ml min^{-1}. After 10 min of large deadspace ventilation, it was slightly increased to 984 ± 465 ml min^{-1}. It increased to 1087 ± 447 ml min^{-1} when V_D^{small} was in use again. These differences were not statistically significant. Corresponding to the unaltered or slightly increased $\dot{V}_A$, carbon dioxide elimination was also virtually unchanged throughout.

Age variations

In the seven patients weighing less than 10 kg, the mean value (± 1 SD) of $\dot{V}_E$ increased by 49% from 1540 ± 500 to 2296 ±796 ml min^{-1}. In the remain-

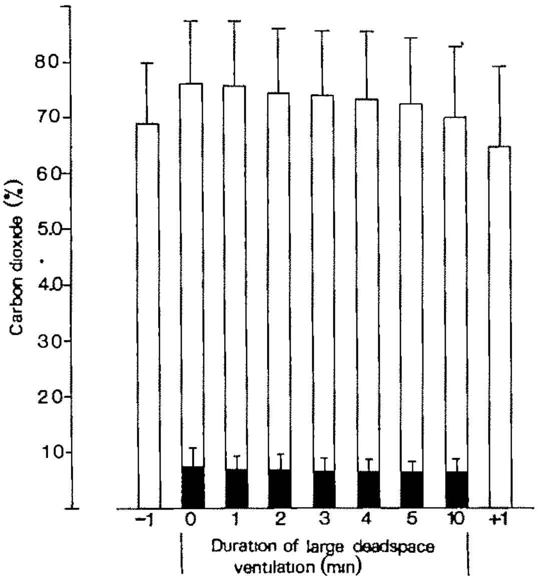

FIG. 2. Mean values + 1 SD of end tidal carbon dioxide concentration (open columns) and of inspired carbon dioxide concentration (plateau $F\text{I}_{CO_2}$) (filled columns) before (–1), during 10 min (0–10) and 1 min after large deadspace ventilation (+1).

ing five patients (> 10 kg) the corresponding increase (37%) was from $\dot{V}\text{E}$ 1683 ± 313 to 2314 ± 786 ml min^{-1} (fig. 5). The end-tidal carbon dioxide concentration (mean ± 1 SD) was virtually unchanged in both weight groups during $V\text{D}^{large}$ ventilation (fig. 5).

Deadspace ventilation ($\dot{V}\text{D}$) at $V\text{D}^{large}$ was, however, more than 250% higher in the younger patients, with a mean value (± 1 SD) of 199 ± 87 ml min^{-1} kg^{-1} below and 76 ± 35 ml min^{-1} kg^{-1} above 10 kg ($P < 0.05$) (fig. 6). This was also reflected by the $V\text{D}/V\text{T}$ ratio, which was greater in the smaller patients ($P < 0.05$) (fig. 6). The inefficient ventilation in the younger patients was also demonstrated by the higher $\dot{V}\text{E}/\dot{V}\text{CO}_2$ ratio ($P < 0.05$) (fig. 6) – a difference that was not seen in the $\dot{V}\text{A}/\dot{V}\text{CO}_2$ ratio.

DISCUSSION

It was not possible to design a system of low deadspace and still incorporate a pneumotachograph. Thus, minute ventilation and tidal volume could not be measured before and after large deadspace ventilation $\dot{V}\text{E}$ and $V\text{T}$ calculated from breaths number 5–10 of $V\text{D}^{large}$ ventilation were used as a basis for the evaluation of the ventilatory response to increased deadspace. At a flow rate of 7 litre min^{-1}, which was the highest met with in this study, the resistance of the system was 3.5 cm H_2O litre^{-1} s^{-1} for $V\text{D}^{small}$ and 7.0 cm H_2O litre^{-1} s^{-1} for $V\text{D}^{large}$. Related to the normal nasal airway resistance in neonates of about 18–20 cm H_2O litre^{-1} s^{-1}, and to the total airway resistance of a 10-kg child, the difference in the system resistances was thought to be too small to affect the results. In a technical assessment of the paediatric *v.* the adult airway adaptor of the capnograph used in this study, it was observed that minute ventilation was increased when the airway resistance was decreased by changing from the paediatric to the adult adaptor (Lindahl, 1984). Furthermore, a subsequent study of the effect of changing the airway resistance in a comparable group of children has shown that an increase in resistance of this order of magnitude does not produce the response seen in this study (Lindahl and colleagues, in preparation).

In the present study, the influence of biological variation was minimized by comparing the responses of each child to changes in deadspace volume. No measurements were made until a clini-

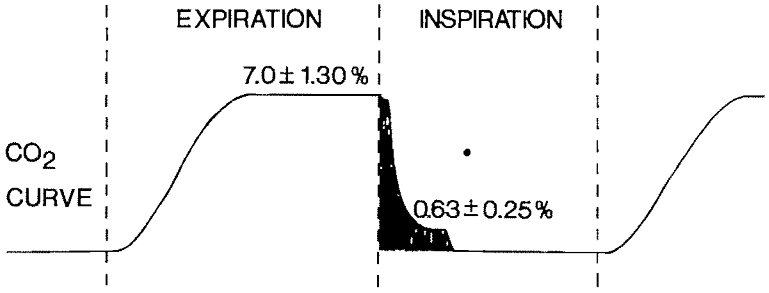

FIG. 3. The schematic carbon dioxide curve showing the typical pattern for rebreathing during large deadspace ventilation. Mean values (± 1 SD) of ET_{CO_2} and inspired carbon dioxide (plateau $F\text{I}_{CO_2}$) concentration after 10 min with $V\text{D}^{large}$ are given.

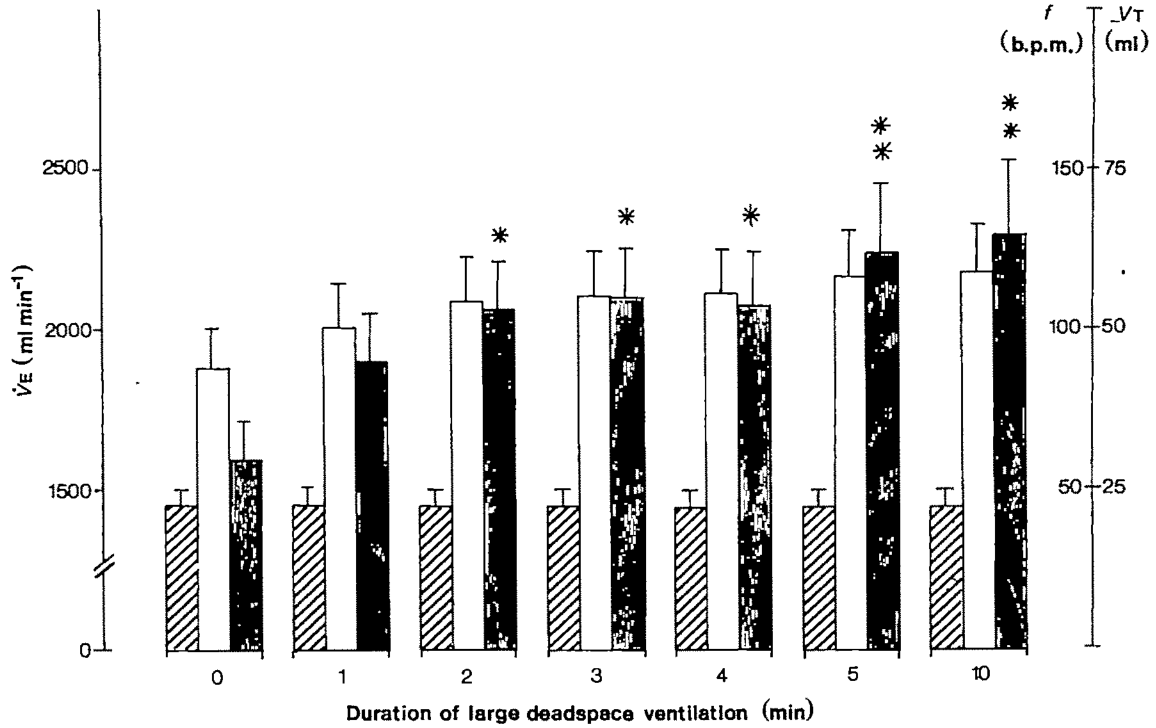

FIG. 4. Mean values (+ 1 SD) of minute ventilation ($\dot{V}_E$, filled columns), tidal volume V_T, unfilled columns) and respiratory rate (f, cross-hatched columns) during 10 min of large deadspace ventilation. $*P < 0.05$; $**P < 0.01$.

cally stable level of anaesthesia and surgery had been reached. This was confirmed by the stability of arterial pressure and heart rate throughout the actual measurements. The reduction in inspired alveolar halothane concentrations caused by increased apparatus deadspace did not appear to be of clinical

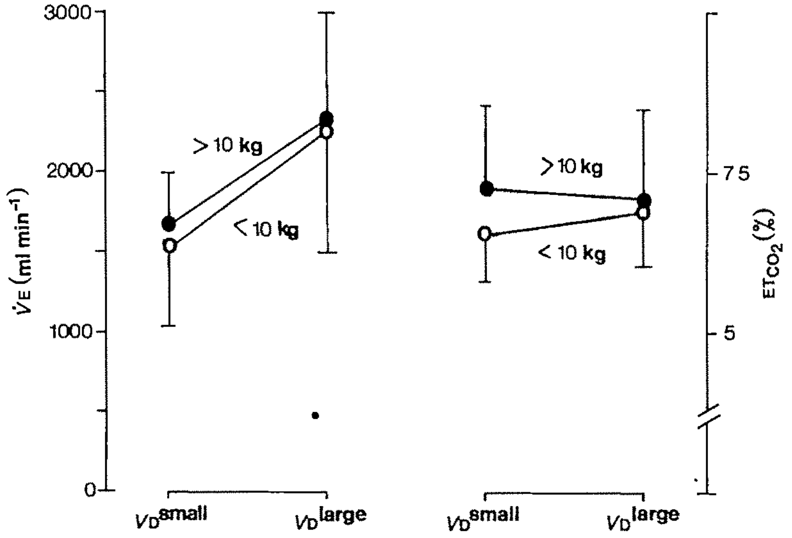

FIG. 5. $\dot{V}_E$ and $E_{T_{CO_2}}$ (mean ± 1 SD) for children less than (open circles) and greater than (closed circles) 10 kg during small (V_D^{small}) and large (V_D^{large}) deadspace ventilation.

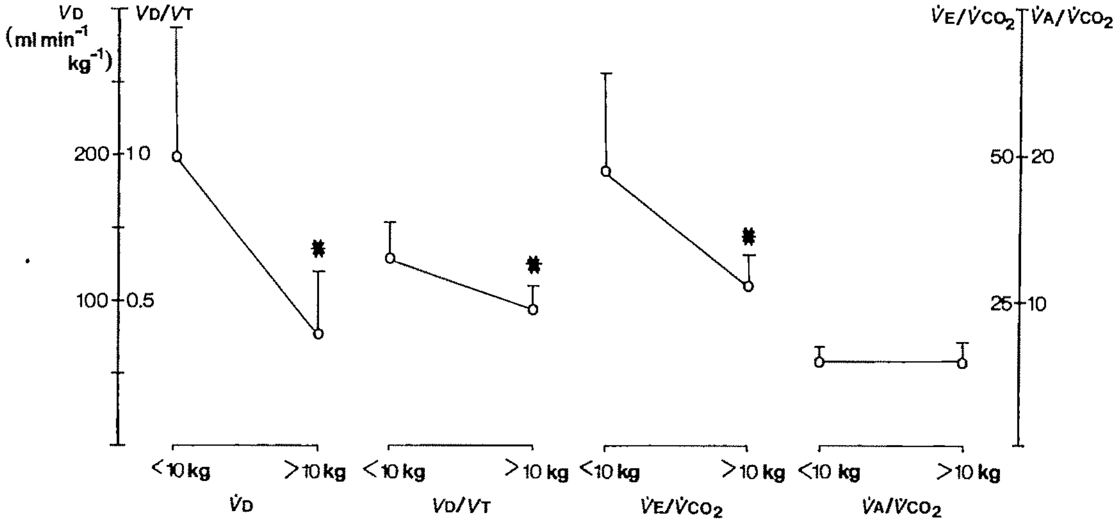

FIG 6. Mean values at V_D^{large} (+ SD) of deadspace ventilation ($\dot V_D$) related to body weight, and of the ratios V_D/V_T, $\dot V_E/\dot V_{CO_2}$, and $\dot V_A/\dot V_{CO_2}$ for children < 10 kg and > 10 kg. *$P < 0.05$.

significance.

In all children the ET_{CO_2} increased when the large deadspace was added. This change was almost instantaneous and so could not have a metabolic cause. Higher ET_{CO_2} concentrations could also be caused by the presence of carbon dioxide in inspired gas. Inspired carbon dioxide was characterized by an initially high concentration early in inspiration, which then rapidly declined to a well identified short plateau phase (fig. 3). This could have been explained by a low fresh gas flow and thus represent rebreathing, not only from the added deadspace, but also as a result of low FGF; but rebreathing caused by inadequate fresh gas flows occurs late in inspiration (Lindahl, Charlton and Hatch, 1985) and was not seen in any patient in the present series. Besides, the formula used for setting the FGF was found to give an adequate FGF (Lindahl, Charlton and Hatch, 1984). Hence, rebreathing as a result of a low fresh gas flow was unlikely. The presence of a short plateau phase may be a reflection of a gas-mixing interface between alveolar gas and fresh gas from the T-piece. Simultaneously with the increase in mean ET_{CO_2} of 0.72% immediately after the start of V_D^{large} ventilation, the mean plateau of inspired carbon dioxide was 0.74%. This makes the value of the inspired carbon dioxide concentration a likely explanation for the increased ET_{CO_2} concentrations. During the period of V_D^{large} ventilation, inspired plateau concentrations of carbon dioxide and ET_{CO_2} decreased gradually as a result of compensatory ventilatory mechanisms.

All patients increased their minute ventilation in response to the larger deadspace by increasing tidal volume; respiratory rate did not change. At 10 min, ET_{CO_2} had been restored to the values found during V_D^{small} ventilation. Hypoxia is an unlikely explanation for this response since, although the inspired oxygen tension is reduced in early inspiration, the small size of the added deadspace in relation to the tidal volume, and the high F_{IO_2} (0.5), would have preserved a high alveolar oxygen tension. Furthermore, hypoxic drive is reduced during halothane anaesthesia (Hirshman et al., 1977). A more likely causal factor is carbon dioxide rebreathing. However, studies of carbon dioxide rebreathing during halothane anaesthesia in children produced by both low fresh gas flow (Byrick, 1980; Lindahl, Charlton and Hatch, 1985) and the addition of 2% and 4% carbon dioxide to an adequate FGF (Olsson and Lindahl, 1985) have failed to show the uniform response demonstrated in this study. The pattern of exposure to carbon dioxide differs in these three types of carbon dioxide rebreathing. In the large deadspace situation the first part of the inspired gas is almost identical to alveolar gas. An attractive but hypothetical explanation for the response to increased deadspace is that pulmonary reflexes, sensitive to oxygen or carbon dioxide tensions, are terminating inspiration at a higher volume because of the continued presence of alveolar gas tensions in the airways during the early part of inspiration. This would explain both the uniformity of response and the fact that the increase in mean tidal volume of 14.6 ml was almost equal to the extra deadspace added.

Although the ventilatory response to the large deadspace was adequate in the smaller patients, ventilatory efficiency was decreased significantly. The mean deadspace ventilation (ml min^{-1} kg^{-1}) was more than 250% higher than in the children weighing more than 10 kg. $V\text{D}/V\text{T}$ ratios were also higher in the smaller patients and the ventilatory efficiency expressed by the $\dot{V}\text{E}/\dot{V}\text{CO}_2$ ratio was significantly reduced (fig. 6). Thus, apparatus deadspace is of relatively greater importance in younger children since proportionately higher volumes of ventilation are required to eliminate carbon dioxide.

It was concluded that, when the apparatus deadspace was increased from 2 to 16 ml in spontaneously breathing children, the ventilatory response was adequate in all patients as far as minute ventilation, end-tidal carbon dioxide concentration, alveolar ventilation and carbon dioxide elimination were concerned. The ventilatory efficiency was, however, significantly worse in the patients weighing less than 10 kg, emphasizing the need to minimize apparatus deadspace during spontaneous breathing in children. Furthermore, the results suggest the liberal use of controlled ventilation during anaesthesia and surgery on these smaller children.

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CHANGES IN VENTILATORY PATTERNS DURING HALOTHANE ANAESTHESIA IN CHILDREN

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Halothane is the most commonly used anaesthetic agent in paediatric anaesthesia (Reynolds, 1962; Krivosic-Horber, Sauvage and Calmes, 1973; Govaerts and Sanders, 1975) and, like all halogenated hydrocarbon anaesthetics, depresses ventilation (Munson, 1972) — an effect dependent on the age of the patient (Lindahl, Olsson and Thomson, 1981) and on the alveolar concentration of the anaesthetic (Munson et al., 1966). However, few studies are available which detail the changes in ventilatory patterns during halothane anaesthesia in children (Wilson and Harrison, 1964). This paper describes measurements of minute ventilation ($\dot{V}$E), tidal volume (VT), respiratory frequency (f), mean inspiratory flow (VT/TI), inspiratory timing (TI/T^{tot}) and end-tidal carbon dioxide tension (PE$'_{CO_2}$) in 12 children weighing between 10 and 20 kg. The measurements were made at increasing inspired concentrations of halothane.

SUMMARY

Changes in ventilatory variables ($\dot{V}$E, VE, f, TI/T^{tot}, VT/TI, PE$'_{CO_2}$) were studied in 12 unpremedicated children, weighing between 10 and 20 kg, during halothane anaesthesia. At an inspired concentration of 0.5% halothane, respiratory rate increased, VT decreased, and $\dot{V}$E did not change markedly. When the inspired halothane concentration increased further, there was a significant decrease in $\dot{V}$E, mainly as a result of a marked decrease in VT. PE$'_{CO_2}$ increased significantly and inspiratory duty cycle decreased at high inspired halothane concentrations. On return to baseline (0.5% halothane), there was a significant decrease in inspiratory timing and a significant increase in PE$'_{CO_2}$. The relations between these changes and the effect of halothane on inspiratory muscles are discussed.

PATIENTS AND METHODS

Twelve children, scheduled for elective minor surgical procedures, were studied. Mean (± SD) age was 39 ± 17 months (range 20–68 months), weight 15 ± 2.9 kg (range 10.5–20 kg) and height 96 ± 11.5 cm (range 77–111 cm). All patients were healthy, were taking no medication and had normal cardiopulmonary function. Parental consent was obtained after full explanation before anaesthesia. None of the children included in this study was premedicated. The study was performed either immediately before surgery (eight children), or during the period after operation (four children) if no anaesthetics apart from halothane and nitrous oxide had been used during the surgical procedure.

Anaesthesia was induced with oxygen and nitrous oxide in equal parts (FI$_{O_2}$ 0.5) and 2–2.5% halothane using an appropriate mask and an open circuit with a non-rebreathing valve. Intubation was performed without neuromuscular blockade under appropriate inspired halothane concentration (uncuffed endotracheal tube). The total fresh gas flow was identical for all patients (oxygen 4 litre, nitrous oxide 4 litre) throughout the study, and was sufficient to prevent rebreathing (Lindahl, Hulse and Hatch, 1984). After tracheal intubation, the inspired concentration of halothane was decreased to 0.5%; the children were breathing spontaneously.

Rectal temperature was monitored and maintained between 36.5 and 37.5 °C for all children. The ECG was monitored continuously.

The tidal volume (VT) was measured by integrat-

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ing the flow signal obtained from a Fleish No. 0 pneumotachograph with an internal volume of 4.7 ml connected to a Godart differential pressure transducer. The pneumotachograph was placed between the endotracheal tube and a non-rebreathing valve with a low opening pressure (Dighby-Leigh). The fraction of carbon dioxide in the expired gas ($F\text{E}_{\text{CO}_2}$) was monitored continuously in the tracheal tube by a capnograph with automatic correction for nitrous oxide (Datex). The rate of sampling was 50 ml min^{-1}.

The study was divided into four different periods. In the first period, the children were maintained at an inspired concentration of halothane of 0.5% for at least 15 min and a recording of respiratory patterns obtained, breath-by-breath for 1 min (T_0). Then, the inspired halothane concentration was increased to 1% for 10 min and measurements obtained for 1 min (T_1). The inspired halothane concentration was increased again, to 1.5% for 10 min (T_2). Finally, the inspired halothane concentration was decreased to 0.5% for 15 min. This last period, called T'_0, was studied to determine individual variations and eventual consequences of prolonged anaesthesia. Records of $V\text{T}$ and $F\text{E}_{\text{CO}_2}$ were made throughout the study, but breath-by-breath recordings were performed only during the 1 min at the end of each period. The children were not stimulated in any way throughout the period of study.

At each inspired halothane concentration, the durations of inspiration ($T\text{I}$), expiration ($T\text{E}$) and total breathing cycle (T^{tot}) were measured by averaging 10 successive breaths.

The following respiratory variables were calculated: minute ventilation $\dot{V}\text{E}$ (ml min^{-1} kg^{-1}), respiratory frequency (f), mean inspiratory flow ($V\text{T}/T\text{I}$) (ml kg^{-1} min^{-1}), inspiratory duty cycle ($T\text{I}/T^{\text{tot}}$) and end-tidal carbon dioxide partial pressure ($P\text{E}'_{\text{CO}_2}$) (kPa).

Carbon dioxide output ($\dot{V}\text{CO}_2$) was calculated for each period using the following formula:

$$\dot{V}\text{CO}_2\,(\text{ml min}^{-1}) = \frac{\dot{V}\text{E} \times F\text{E}_{\text{CO}_2}}{100}$$

$F\text{E}_{\text{CO}_2}$ is the expired carbon dioxide fraction. $\dot{V}\text{E}$ was corrected to body temperature and pressure saturated (BTPS), $\dot{V}\text{CO}_2$ values to ambient temperature and pressure saturated (ATPS).

Statistical evaluation of the data utilized a two-way analysis of variance between the four periods of the study and the two-tailed t test for paired samples. P values < 0.05 were regarded as significant. The values are expressed as mean ± standard error of the mean (SEM).

RESULTS

Values (mean ± SEM) of $\dot{V}\text{E}$, $V\text{T}$, f, $\dot{V}\text{T}/T\text{I}$, $T\text{I}/T^{\text{tot}}$, $P\text{E}'_{\text{CO}_2}$ $\dot{V}\text{CO}_2$, obtained at various inspired concentrations of halothane are shown in table I. Values at T_0 were not significantly different between the chil-

TABLE I. *Ventilatory variables (mean ± SEM) at various inspired concentrations of halothane. Comparisons are made between the initial period* T_0 *and the other periods,* T_1 T_2 *and* T'_0. $^{***}P < 0\ 001$; $^{**}P < 0.01$; $^{*}P < 0\ 05$

	Inspired halothane concentration (%)			
	0.5 Period T_0	1 Period T_1	1.5 Period T_2	0.5 Period T'_0
$\dot{V}\text{E}$ (ml kg^{-1} min^{-1})	148.22 ±6.74	129.90*** ±7.79	113.40*** ±5.99	140 8* ±6.85
$V\text{T}$ (ml kg^{-1})	4.98 ±0.36	4.11*** ±0.29	3.34*** ±0.25	5.06 ±0.34
f (b.p.m.)	31.76 ±2.52	32.75 ±2.45	35.36*** ±2.66	28.76 ±1.94
$T\text{I}/T^{\text{tot}}$	0.55 ±0.02	0.53 ±0.02	0.52* ±0.01	0.52* ±0.02
$P\text{E}'_{\text{CO}_2}$ (kPa)	5.2 ±0.19	5.5*** ±0.22	6.1*** ±0.23	5.3** ±0.19
$V\text{CO}_2$ (ml kg^{-1} min^{-1})	743 ±20.1	692 ±23.7	682*** ±22.5	741.5 ±26.4
$V\text{T}/T\text{I}$ (ml kg^{-1} min^{-1})	272.7 ±12.9	243.4*** ±14.4	217.7*** ±11 6	262.5 ±13

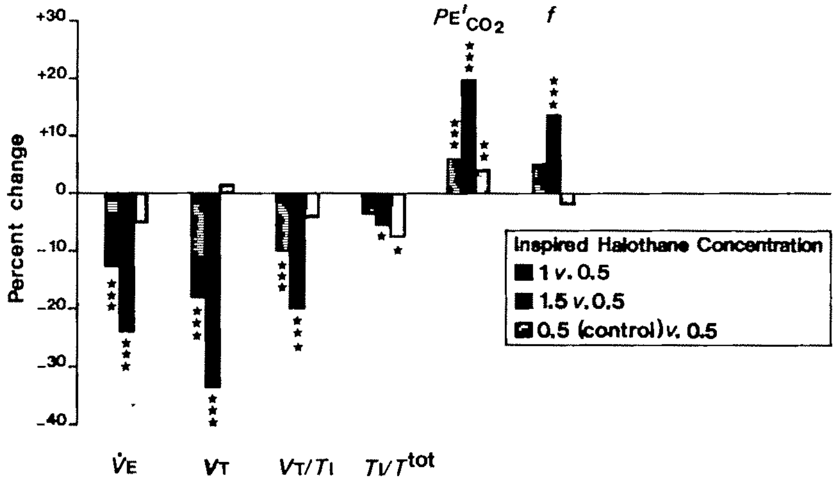

FIG. 1. Per cent change in ventilatory variables, expressed as per cent of the initial value (Period T_0). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

dren studied before operation and those studied after operation. Carbon dioxide output was statistically linked to weight ($P < 0.001$), height ($P < 0.001$) and age ($P < 0.001$).

The changes in the ventilatory patterns at various depths of halothane anaesthesia are summarized in figure 1. There was a significant decrease in $\dot{V}$E when the inspired concentration of halothane increased, mainly as a result of a significant decrease in VT. The increase in respiratory rate was significant between 0.5 and 1.5%, but no increase was found between 0.5 and 1%. Changes in effective respiratory timing were significant between 0.5 and 1.5% halothane. Mean inspiratory flow decreased significantly with increasing depth of halothane anaesthesia. Changes in PE'_{CO_2} were also related to changes in inspired halothane concentration, but the increase obtained between 1 and 1.5% was about twice that obtained between 0.5 and 1%. $\dot{V}CO_2$ decreased significantly only between 0.5 and 1.5% inspired halothane concentration. The control period was marked by a significant decrease in inspiratory timing and an increase in PE'_{CO_2}, but no significant change in VT, respiratory rate, mean inspiratory flow or $\dot{V}CO_2$.

DISCUSSION

Few data are available on normal ventilatory patterns in children younger than 6 years of age, probably because of difficulties in obtaining real co-operation at this age.

In comparison with normal data for awake children (Crone, 1983), the respiratory rate at T_0 was markedly increased, tidal volume was decreased, but minute ventilation did not change markedly. The end-tidal carbon dioxide tension was at the normal upper range limit for age, and mean values for $\dot{V}CO_2$ were similar to published data for anaesthetized children (Nightingale and Lambert, 1978; Lindahl, Olsson and Thomson, 1981; Lindahl, Hulse and Hatch, 1984), and not different from those obtained by Lewis, Dural and Iliff (1943) in awake children. The effect on the respiratory patterns, of the use of nitrous oxide in this study, is difficult to delineate. Nitrous oxide has been shown to have either a mild stimulant effect (Eckenhoff and Helrich, 1958) or a ventilatory sparing effect (Hornbein et al., 1969). In children, Salanitre and Rackow (1976) demonstrated a decrease in $\dot{V}$E during halothane anaesthesia with 70% nitrous oxide when compared with 3% nitrous oxide. However, a mixture of nitrous oxide, oxygen and halothane is generally used during general anaesthesia to reduce the MAC of halothane, and this study was essentially performed to define the changes in ventilatory patterns under general anaesthesia with halothane in children.

An increase in inspired halothane concentration produced significant decreases in VT, $\dot{V}$E and VT/TI, with a significant increase in PE'_{CO_2}. Thus, the increase in inspired halothane concentration produced, as previously reported in adults (Devine, Hamilton and Pittinger, 1958; Larson et al., 1969; Munson et al., 1966), a marked decrease in alveolar ventilation. In children, Wilson and Harrison (1964) found, as we did, a marked decrease in $\dot{V}$E and VT, but only a mild difference in mean respiratory rate during halothane anaesthesia and recovery from anaesthesia. Decrease in $\dot{V}\text{CO}_2$ at high inspired halothane concentration is most likely the result of a large decrease in effective alveolar ventilation. The decrease in tidal volume seems to result from a central action of halothane, which has a primary direct action on the central regulatory and integratory mechanisms (Ngai, Katz and Farhie, 1965). The significant decrease in mean inspiratory flow reflects a decrease of the rate of increase of the centrally generated inspiratory activity (Gautier, 1980). The effect of halothane on respiratory rate is less well known. In agreement with the results recently reported in cats (Nishino et al., 1984), our study demonstrated a decrease in the timing of the inspiratory drive during halothane anaesthesia. This effect was true essentially for high inspired concentrations and suggests that there was a direct effect of halothane on inspiratory muscles.

Using the return to baseline concentration (T'_0), individual variations can be assessed and the role of the duration of anaesthesia characterized. We did not find any significant change in $V\text{T}$, $\dot{V}\text{CO}_2$, $V\text{T}/T\text{I}$ and respiratory rate between T_0 and T'_0. However, there was a significant decrease in inspiratory duty cycle and a significant increase in $P\text{E}'_{\text{CO}_2}$ between the two periods. Changes in inspiratory timing may result from a direct effect of halothane on inspiratory muscles with progressive recovery. Changes in $P\text{E}'_{\text{CO}_2}$ are also related to work output of inspiratory muscles (Milic-Emili and Tyler, 1963). Indeed, the duration of anaesthesia does not seem to influence carbon dioxide response curves in the dog and the increase in $P\text{E}'_{\text{CO}_2}$ cannot be explained by changes in the carbon dioxide sensitivity (Brandstater, Eger and Edelist, 1965). In this study, the duration of anaesthesia did not change $\dot{V}\text{CO}_2$ either, although carbon dioxide production increased with inspiratory muscle fatigue (Macklem, 1980). Thus, the changes in respiratory variables we have observed in this study may be an additional reason for assisting ventilation in children undergoing surgical procedures of long duration (Hulse, Lindahl and Hatch, 1984) to avoid prolonged ventilatory depression and possible alterations in muscle activity.

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RECTAL INDUCTION OF ANAESTHESIA IN CHILDREN WITH METHOHEXITONE

Patient Acceptability and Clinical Pharmacokinetics

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SUMMARY

Rectal induction of anaesthesia with 10% methohexitone 100 mg ml^{-1} was used in 50 healthy children, using a standard dose of 25 mg/kg body weight. The absorption of methohexitone was rapid and reliable: the children fell asleep within 10–15 min. The plasma concentration peaked at 10–15 min and then decayed rapidly. The terminal half-life of rectal methohexitone was 1–2 h. Overall patient acceptability was good, and there were no major complications.

Methohexitone is a short-acting induction agent usually administered i.v. However in children the rectal route may be preferable, to minimize the possible psychological trauma of anaesthesia, since rapid systemic absorption is achieved when this drug is given as an aqueous solution of the sodium salt. Budd, Dornette and Wright (1965) commented on the rapidity of recovery, and on the suitability of methohexitone for use in the outpatient. However, uncertainty about the appropriate dose required to induce sleep has led to the use of different doses ranging from 10 to 50 mg/kg body weight (Orallo and Eather, 1965; Goresky and Steward, 1979), although Liu, Goudsouzian and Liu (1979), who used methohexitone as a rectal premedicant in doses of 20, 25 and 30 mg kg^{-1}, found no significant differences in the times to the onset of sleep.

The purpose of this uncontrolled study was to document, through the use of a questionnaire, the reactions of child and parent to the induction of anaesthesia using rectal methohexitone, and to investigate the pharmacokinetics of the rectal administration of the drug.

PATIENTS AND METHODS

Fifty healthy children, weighing 5–23 kg (average weight 17.5 kg), and aged between 8 months and 6 yr, undergoing minor surgery, took part in this study. Informed consent was obtained from their parents. Consent was also given by the Norwegian Medicines Control Authority.

Premedication, consisting of morphine 0.15 mg kg^{-1}, hyoscine 0.01 mg kg^{-1} and diazepam 0.5 mg kg^{-1} (mixed in the same syringe) was given rectally, 30–60 min before induction. A standard 6-cm rectal applicator, coated with 2% lignocaine gel, was used. A preceding cleansing enema was not performed.

A freshly prepared aqueous solution of 10% methohexitone sodium was used. The dose was generally 25 mg kg^{-1}; however, a maximum dose of 500 mg was never exceeded. Anaesthesia was induced with the children lying on their side in bed or in their parents' arms, and they were allowed to remain so until they fell asleep. The patients were judged to be sleeping when they did not respond to their names or the corneal reflex was absent, or both. The patient was then moved onto the operating table, where anaesthesia was maintained with either halothane or enflurane and nitrous oxide in oxygen (FI_{O_2} 0.3). The trachea was intubated in 21 patients as required by the surgical procedures. Ventilation was spontaneous, except in three patients (dental) in whom the lungs were ventilated artificially because of prolonged surgery. All patients received an infusion of lactated Ringer's solution or dextrose 5 ml kg^{-1} h^{-1} i.v. during the operation. Pethidine 1 mg kg^{-1} was administered i.m. to 14 of the children before recovery to minimize discomfort after

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operation. Nine children who were willing to co-operate were selected for the determination of methohexitone plasma concentrations. A peripheral vein was cannulated before induction. Approximately 3 ml of blood was withdrawn at appropriate intervals after the rectal administration of the methohexitone. After centrifugation, the plasma was deepfrozen until analysis could be performed. The longest period of storage was 2 weeks. The concentration of methohexitone in the plasma was determined by high pressure liquid chromatography (Björkman and Idvall, 1984). The coefficient of variation of this method is approximately 3% for methohexitone concentrations down to 62 ng ml^{-1}.

After the operation, the children were returned to the recovery ward where they were observed, and any adverse reaction noted. All patients were given oxygen through a nasal catheter. Recovery was considered complete when the patients opened their eyes to command. All day-case patients were able to drink or take a light meal before discharge.

To assess patient/parent acceptability, a questionnaire was given to each parent, to be returned to the authors after 1 week.

RESULTS

Forty-two patients were day cases (84%) and eight inpatients. Two patients in the day-case group stayed overnight at the hospital, one because of dental bleeding, and the other because of inadequate pain relief after surgery. No day-case patients required a prolonged hospital stay because of over-sedation.

The average time from premedication to induction of anaesthesia with methohexitone was 33 min (SD 21 min).

In no patient was the sedation considered too heavy.

After the administration of methohexitone, 46 patients (92%) were asleep within 15 min (average 9.1, SD 3.6 min). Three children were not asleep by 15 min. One of these fell asleep by 20 min without further medication. The other two children were both relaxed and accepted the face mask without difficulty. One of these was in the pharmacokinetic study (patient No. 2, table I). A fourth child showed little sign of sedation 10 min after an induction dose of methohexitone 25 mg kg^{-1}. He received a further 8.3 mg kg^{-1} and was asleep by 15 min.

Only one patient defaecated immediately after rectal induction. He was given a further dose and was asleep within 10 min.

Laryngospasm was not noted, although hiccup was observed in the patient who had received methohexitone 25 mg + 8.3 mg kg^{-1}.

The mean operating time in the 50 patients was 41 min (SD 28 min). Heart rate and arterial pressure were acceptable in all patients. There were no complications.

The mean time from the end of anaesthesia to full recovery was calculated with the patients divided into two groups: those who had received pethidine during the anaesthesia or in the period immediately after operation, and those who had not. Mean recovery time in the pethidine group (14 patients) was 90 min (SD 48 min), and for the "no pethidine" group (36 patients) 43 min (SD 16 min) ($P = 0.4$).

Completed questionnaires were received from the parents of 47 children (table II). None of the four children who were slow to respond to rectal induction reported any recall or "bad dreams". Three parents spontaneously added to the questionnaire

TABLE I. *Pharmacokinetic data from nine children given rectal methohexitone *As methohexitone sodium. One milligram of the salt corresponds to 0.92mg of free acid †She was calm and sedated, but did not fall asleep. ‡The final plasma concentration values did not fit a straight line in the semilogarithmic plot (see fig. 2)*

Patient No.	Weight (kg)	Sex	Dose* ($mg\ kg^{-1}$)	Time to loss of consciousness (min)	Methohexitone peak concentration Time (min)	Methohexitone peak concentration ($\mu g\ ml^{-1}$)	Methohexitone half-life (min)
1	25	F	20	5	15	2.8	121
2	15	F	25	†	15	0.85	103
3	22	F	23	6	10	2.8	98
4	21	M	24	7	15	3.9	96
5	22	F	23	10	15	1.8	100
6	14	M	21	10	20	3.4	72
7	16	F	25	6	14	3.5	‡
8	21	F	24	5	10	3.3	130
9	21	M	21	6	20	3.2	98
Mean (SD)	20 (3.7)		23 (1.8)	7 (2.0)	15 (3.6)	2.8 (1 0)	102 (17)

TABLE II. *Questionnaire and answers. Parents were specifically requested to go through and discuss the questions with children who were older than 3 years of age, in order to obtain more objective answers*

Question	*n*	Yes	(%)	No	(%)
(1) Was the child afraid to be anaesthetized (before coming to hospital)?	45	8	18	37	88
(2) Has the child been anaesthetized previously?	46	15	33	31	67
(3) If "yes", was the child more relaxed this time?	—	—	—	—	—
(4) Do you (parent) think it was "unethical" to use the rectal route for induction of anaesthesia?	45	0	0	45	100
(5) Can the child remember anything about going off to sleep?	46	10	22	36	78
(6) If "yes", was it					
(a) very unpleasant?	10	0	0		
(b) unpleasant?	10	1	10		
(c) pleasant?	10	6	60		
(d) very pleasant?	10	3	30		
(7) Did the child have any "bad dreams" after the operation?	47	4	9	43	91
(8) If "yes", when:					
(a) first night?		3	75		
(b) first 3 nights?		1	25		
(c) first week?		0	0		
(9) Would you (or your child) be happy to have the same anaesthetic technique on a subsequent occasion?	47	47	100	0	0

their comment of "excellent" regarding the rectal induction. One of the children had been given inhalation induction on a previous occasion.

The plasma concentrations of methohexitone against time are shown in figures 1 and 2. The pharmacokinetic characteristics of the drug in the nine patients are given in table I. The mean peak concentration was 2.8 μg ml^{-1} (11 μmol litre^{-1}) 15 min after rectal administration. The children lost consciousness during the initial rapid distribution of the drug and, less than 10 min after this, the plasma concentration curves began to decay. The mean elimination half-life of methohexitone was 102 min.

DISCUSSION

The available techniques for the induction of anaesthesia in children fall into four categories: inhalation, intravenous, intramuscular and rectal. However, since many children do not like, or are afraid of the mask, inhalation induction may be a stormy affair. Kay (1966) has shown a positive linear correlation between the apparent distress before induction and postoperative psychological trauma in children. Benson and Reinand (1960) found that psychological disturbance after operation was much

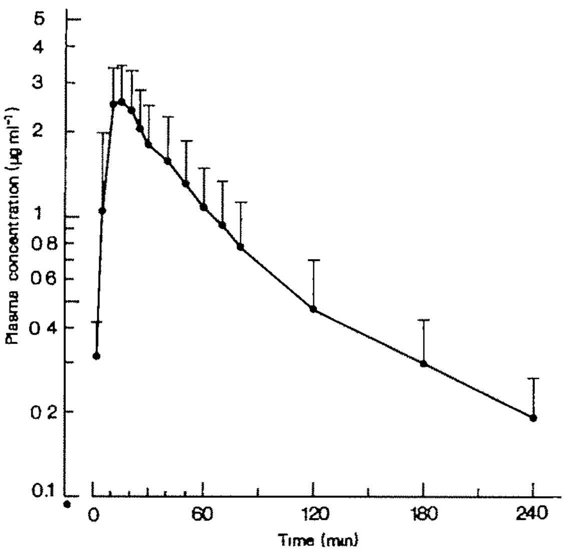

FIG. 1. Mean plasma concentration curve of methohexitone after rectal administration in nine children. The bars mark the standard deviation in each point. Because of difficulties in blood sampling before the induction of anaesthesia, the first three points are based on two, five and six measurements only.

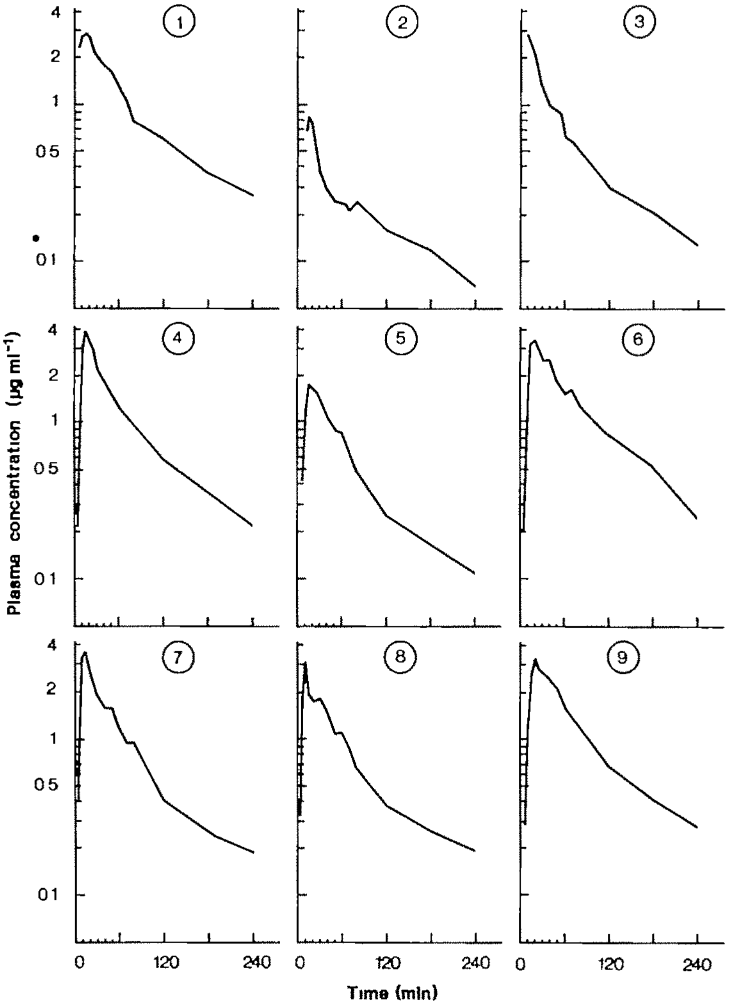

FIG. 2. Individual plasma concentration curves of methohexitone after rectal administration in nine children.

more frequent after inhalation than after rectal induction. Meyers and Muravchick (1977) concluded that the "asleep" induction technique causes less behavioural upset than "awake" techniques.

Fear of needles and injections is common amongst children. Hodges (1960), reported that i.v. induction was less favoured than inhalation induction in the children he examined, and that fewer children would accept a further induction by this route.

The disadvantages of rectal administration include interruption of absorption by defaecation. Moreover, in some countries or groups, lack of acceptability by the patients or their parents might make the choice of the rectal route difficult. In this study, only one patient defaecated, but anaesthesia was induced satisfactorily with a second administration. In Scandinavia, rectal thermometry is practised widely; thus, rectal induction can be explained simply as "just like taking the temperature". In this series the patient/parent acceptability was 100%. Saint-Maurice and colleagues (1979), using rectal ketamine, have reported similar findings.

Four out of 47 children (8.5%) in this series had "bad dreams", three of them during the first night after operation. This is similar to the frequency reported by Horne and Ahlgren (1973) following various inhalation agents (8–10%). Nine of the 10 children who could remember going to sleep recalled the experience as "pleasant" or "very pleasant", and only one child described it as "unpleasant".

After rectal induction with methohexitone, Budd, Dornette and Wright (1965) reported a 17.5% incidence of complications, ranging from tremors to laryngospasm. Only one patient in our series developed hiccup in association with loss of consciousness. This difference may be explained by the fact that our patients received a premedication of morphine, hyoscine and diazepam before induction. Recovery time can be prolonged when pethidine is used in association with inhalation agents and also after rectal methohexitone (Budd, Dornette and Wright, 1965). In spite of the longer recovery time in our patients who received pethidine, no day-case patients required admission because of oversedation.

To our knowledge, the only other induction agent for which the pharmacokinetics have been studied in association with rectal administration is ketamine (Idvall, Holasek and Stenberg, 1983). Loss of consciousness after ketamine was within 7–15 min, but the plasma concentration continued to increase for another 30 min. It is clear that the absorption of methohexitone is quicker. For methohexitone, as for ketamine, the bio-availability of rectally absorbed drug is low. Using a rectal applicator of 6 cm, probably only a minor part of the rectal solution will be in contact with the mucosa of the lower rectum where venous drainage by-passes the liver (De Boer, De Leede and Breimer, 1984). Thus, the major part of the absorbed drug will pass directly to the liver via the portal vein and will consequently be subject to "first-pass" metabolism. The hepatic extraction ratio (hepatic clearance/hepatic blood flow) of methohexitone is approximately 0.5, which means that one half of the amount of drug that reaches the liver via the portal vein will be metabolized (Hudson, Stanski and Burch, 1983). In spite of this, there is remarkably little interpatient variability in eight of the nine plasma concentration curves. The terminal half-life of methohexitone in our series was 102 min, which is in good agreement with findings in adult volunteers who received methohexitone as an infusion i.v.

In this series, 43 patients (86%) were day cases. Of these, 41 patients were ready to leave the hospital approximately 4–5 h after the induction of anaesthesia. Two patients were admitted for non-anaesthetic reasons. Our findings of a rapid recovery following rectal induction are in agreement with those by Goresky and Steward (1979).

Rectal premedication with diazepam, morphine and hyoscine has been reported previously (Lindahl, Olsson and Thomsom, 1981); our experience is in agreement with their clinical findings.

In conclusion, rectal methohexitone, when given in a dose of 25 mg kg^{-1}, is a safe, acceptable and relatively rapid means of inducing anaesthesia. Its use is applicable to day-case and inpatient surgery, provided adequate recovery facilities are available.

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EFFECTS OF THE RECTAL ADMINISTRATION OF DIAZEPAM

Diazepam Concentrations in Children Undergoing General Anaesthesia

H. SONANDER, E. ARNOLD AND K. NILSSON

SUMMARY

Diazepam 1 mg/kg body weight was administered rectally to 14 children (11–22.5 kg) before minor surgery under general anaesthesia. Administration in solution (n = 7) resulted in a rapid increase in serum concentrations which were maintained for 8 h. Administration by suppository (n = 7) resulted in significantly lower serum concentrations at 10 and 20 min, but higher concentrations at 2 h. At other intervals the concentrations did not differ from those reached after administration of diazepam in rectal solution. These results favour the use of a solution when rectal diazepam is used for premedication in children.

Pharmacokinetic studies have compared parenteral and various rectal preparations of diazepam in adults (Moolenaar et al., 1980; Magnusson et al., 1979) and children (Meberg et al., 1978) and indicated that systemic concentrations increase rapidly and are well maintained after rectal administration. Such a profile is of interest to the anaesthetist as it will provide a rapid increase to sedative concentrations for premedication and an effect which will last into the period after operation. We have studied serum concentrations of diazepam for 24 h after its rectal administration, in solution or by suppository, to children undergoing general anaesthesia.

PATIENTS AND METHODS

Following consent from the parents and the approval of the local Ethics Committee, 14 children (aged 1.5–8 yr) weighing 11–22.5 kg (mean 16.9 kg) were given diazepam before minor surgery (mainly squint operations). Seven were given a solution (solvent: propyleneglycol) through a rectal tube (Stesolid, AS Dumex) and seven received suppositories (Stesolid supp., AS Dumex). No special precautions were taken to keep the drug in the rectum. A dose of 1 mg/kg body weight, adjusted to the nearest 5 mg, was used. This resulted in a mean dose of 0.99 mg kg^{-1} (range 0.8–1.2) of the rectal solution and 0.96 mg kg^{-1} (range 0.8–1.1) of the suppositories.

Venous blood was withdrawn before administration and at the following intervals for measurement of serum diazepam concentration: for rectal solution—5, 10, 15, 20, 30, 40, 50 min, 1, 1.5, 2, 4, 8 and 24 h; for suppositories—10, 20, 40 min, 1, 1.5, 2, 2.5, 3, 4, 8 and 24 h. Slight deviations in sampling times occurred and all times are given with the range within which blood sampling was performed. Samples could not be obtained at all intervals in all children. Serum was deep frozen for later analysis of the concentration of diazepam using the gas-chromatographic method described by Arnold (1975). Drugs used during anaesthesia and the period after operation included halothane, thiopentone, pancuronium, trimeprazine, ketamine, paracetamol and salicylic acid. The possibility that any or all of these drugs may have affected the determination of the diazepam concentration was assessed.

Statistical methods

Each serum concentration was standardized to a given dose of 1 mg kg^{-1}, whereafter serum concentrations at corresponding intervals were tested with the Wilcoxon rank sum test (Colton, 1974) at the 95% confidence level with the zero hypothesis that

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there was no difference between the two methods of administration.

RESULTS

The interference measurements did not suggest that the diazepam peaks included any of the other drugs given to the patients.

After the rectal solution the serum concentration of diazepam increased rapidly, whereas suppositories caused a slower increase, but to a higher serum concentration (fig. 1). The suggested sedative value of 150 ng ml^{-1} (Mattila et al., 1981) was exceeded in five of the seven children given the rectal solution at 5 min and in all of them at 10 min. Diazepam concentrations were not measured at 5 min after suppositories, but at 10 min only three of the seven children had serum concentrations greater than 150 ng ml^{-1} and at 40 min one was still below this value.

The rectal solution group had its peak median value of 619 ng ml^{-1} (range 315–945) at 30 min, whereas in the children receiving suppositories, the peak median value of 848 ng ml^{-1} (range 560–1141) was obtained at 2 h ± 15 min. At 10 and 20 min the diazepam concentration after rectal solution was significantly greater than after suppositories, the reverse being the case at 2 h ± 15 min. At all other intervals there were no statistically significant differences between the two methods of administration. The median values after suppositories were, however, higher at all intervals after 1.5 h.

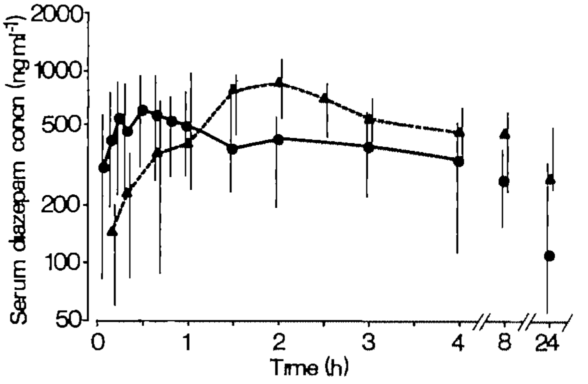

FIG 1. Serum concentrations of diazepam (median and range) in two groups of children ($n = 7$), treated with diazepam 1 mg/kg body weight rectally, either as a solution (●) or as suppositories (▲).

DISCUSSION

Diazepam administered by the rectal route, either as solution or as suppository, produced high but variable serum concentrations, a finding similar to that in other studies (Knudsen, 1977; Dulac et al., 1978; Moolenaar et al., 1980; Mattila et al., 1981). Practical difficulty in administration has been proposed as a possible explanation for this variability, with solution remaining in the rectal tube or being lost from the rectum (Dulac et al., 1978; Magnusson et al., 1979). This may be the case, but in our study variability was great even in the suppository group, where drug loss should be minimal.

The initial serum concentrations found in our study after the administration of the rectal solution are in agreement with the reports of Meberg and colleagues (1978) and Mattila and co-workers (1981), but lower than those obtained by Dulac and associates (1978) who used half our dose. The explanation for the latter result is probably that their patients weighed less than ours. The significantly earlier peak with rectal solution compared with suppositories is also in agreement with previous work (Knudsen, 1977). With regard to the maintenance of the serum concentrations, over a 24 h period our measurements confirm the results from the three children receiving rectal solution in the report by Meberg and colleagues (1978).

In two of five measurements in the children receiving rectal solution and in three of seven children in the suppository group, the concentration at 8 h was higher than at 4 h. In both groups, the values at 8 h did not differ from those at 4 h, indicating a second peak at 6–12 h as reported by Meberg and co-workers (1978) and attributed to reabsorption from the intestinal mucosa after the postoperative ingestion of food (Kortilla, Mattila and Linnoila, 1976). In the adult patients in that study the serum concentrations of diazepam only increased after ingestion of fatty food and not plain water. As our patients only received water in the relevant period, the higher serum concentrations at 8 h were probably the result of stochastic variation. Diazepam in suppository resulted in a peak in serum concentration at 2 h after administration. This is in accordance with the study by Moolenaar and colleagues (1980) in young adults, although the doses given in that study were less than those used here.

If a diazepam suppository is given 30 min before anaesthesia in order to achieve the proposed sedative concentration of 150 ng ml^{-1}, the peak in serum concentration will coincide with the end of the anaesthetic or the early postoperative period, since many surgical procedures in children are rather short. A smaller dose given earlier will decrease this peak, but will make the degree of sedation less predictable. In our opinion the rapid increase and well maintained serum concentrations associated with the use of a rectal solution of diazepam is to be preferred. It also allows a wide variation in administration time and a smooth recovery after minor paediatric surgery.

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COMPARISON OF DIAZEPAM AND MIDAZOLAM FOR SEDATION DURING LOCAL ANAESTHESIA FOR BRONCHOSCOPY

K. KORTTILA AND J. TARKKANEN

SUMMARY

Bronchoscopy was performed in 76 outpatients using local anaesthesia plus diazepam 0.2 mg kg^{-1} i.v. or midazolam 0.05 or 0.1 mg kg^{-1} i.v. Patient co-operation and ease of bronchocopy were good in all patients. Two hours after injection, 67% (diazepam 0.2 mg kg^{-1}), 36% (midazolam 0.05 mg kg^{-1}) and 75% (midazolam 0.1 mg kg^{-1}) of the patients failed to recall the insertion of the bronchoscope. Similarly, when asked on the following day, only 22%, 52% and 8%, respectively, of the patients remembered bronchoscopy. Two hours after sedation, the patients' performances in three psychomotor tests were similar to those measured before sedation in each group, but the patients' ability to stand steadily and walk along a straight line reverted to normal significantly ($P < 0.05$) more slowly in patients receiving midazolam 0.1 mg kg^{-1} than in the patients given diazepam. The results suggest that midazolam offers no advantage over diazepam in terms of speed of recovery of psychomotor function, when doses of similar potency are given for bronchoscopy.

Local anaesthetic techniques are preferable to the use of general anaesthesia in outpatients for procedures such as bronchoscopy, since patients require less supervision in the period after operation (Korttila, 1981). Bronchoscopy under local anaesthesia necessitates reliable sedation of short duration to make the procedure more acceptable to the patient (Korttila et al., 1978a). Hitherto, diazepam has been recommended for such sedation (Editorial, 1976; Korttila, 1980a). Recently, it has been suggested that the relatively new benzodiazepine midazolam might be preferable for sedation during short procedures: its effects have been reported to be of shorter duration than those of diazepam (Dornauer and Aston, 1983; Editorial, 1983), its salts are water-soluble, and it causes pain or venous thrombosis only occasionally.

We have previously compared diazepam and flunitrazepam, and have evaluated the relationship between age, amnesia and sedation during local anaesthesia for bronchoscopy (Korttila et al., 1978a, b). Although the suitability of midazolam for use in gastroscopy has been extensively studied (Al-Khudhairi, Whitwam and McCloy, 1982; Brophy et al., 1982; Berggren et al., 1983; Magni et al., 1983), there have been no reports on the utility of midazolam during bronchoscopy. The purpose of the present study was to compare i.v. diazepam and midazolam as amnesic and sedative adjuncts to local anaesthesia for bronchoscopy, with particular attention to the rapidity of recovery after sedation achieved with clinically comparable doses of the drugs.

PATIENTS AND METHODS

Sedation

Seventy-six outpatients undergoing diagnostic, open, rigid bronchoscopy were admitted to the study. The patients were randomly allocated to three groups, which were similar as regards age, weight and height (table I). Any patient who had received a psychotropic drug or any other drug known to interact with benzodiazepines, or who could not perform the recovery tests before the drugs were administered, was excluded. The plan of investigation was approved by our institutional ethics committees, and informed consent was obtained from each patient.

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TABLE I. *Characteristics of test groups (means ± SD), and drug doses injected*

Treatment	No. of patients	Male/ female	Age (yr)	Weight (kg)	Height (cm)
Diazepam 0.2 mg kg^{-1}	27	19/8	55 ± 11	73 ± 12	172 ± 7
Midazolam 0.05 mg kg^{-1}	25	15/10	57 ± 10	59 ± 15	171 ± 6
Midazolam 0.1 mg kg^{-1}	24	14/10	55 ± 11	66 ± 10	168 ± 8

Topical anaesthesia of the respiratory tract was produced by the administration of lignocaine using an ultrasonic nebulizer (Korttila, Tarkkanen and Tarkkanen, 1981). Fifteen millilitre of 4% lignocaine solution was introduced to the nebulizer chamber, and was atomized by oxygen for inhalation. Nebulization was continuous for 15 min during inspiration and expiration. The inhalation anaesthesia was supplemented using three 10-mg aliquots of 10% lignocaine solution, two sprayed into each vallecula and one on the epiglottis. Atropine 0.01 mg kg^{-1} was injected i.v. and, 5 min later, the sedative was administered: diazepam 0.2 mg kg^{-1} was injected to a cubital vein at a rate of 10 mg min^{-1}, or midazolam 0.05 or 0.1 mg kg^{-1} was given at the rate of 5 mg min^{-1}. The patient, the bronchoscopist and the investigator were all unaware of the identity of the drug being administered.

Clinical observations, assessment of amnesia and subjective assessments

Systolic and diastolic arterial pressures were measured by auscultation, and the heart rate was counted at the wrist before, during and after the procedure (Korttila et al., 1978a).

Amnesia was assessed 2 h after injection of the sedative, when each patient was asked if he or she recalled insertion and removal of the bronchoscope. To evaluate the duration of the amnesic effect, we made additional use of two of the tests of clinical recovery: the patients were asked, 1 h and 2 h after injection of the sedative, if they could remember that their ability to stand steadily had been tested at 30 min, and their ability to walk along a straight line at 60 min, respectively.

The bronchoscopist rated both the adequacy of anaesthesia and patient co-operation (ease of bronchoscopy) using visual analogue scales from poor to good. The patient rated the acceptability of the procedure in the same manner.

Evaluation of recovery

The clinical recovery of the patient was determined using Romberg's test and by the patient's ability to walk along a straight line (Korttila, 1976). Assessments were made when the patient arrived in the operating theatre and 30, 60 and 120 min after the injection of the sedative.

Visualization test (James, 1969). The subject was required to trace each of 10 intermingled lines from their origins on the left side of a page to their termination on the right, without the aid of a finger. The score was the number of correct tracings per 3-min period.

Aiming test (James, 1969). A piece of paper (20 cm × 30 cm) with 15 rows of 20 open circles (diameter 2 mm) was used. The subject had to place a dot inside each of as many circles as possible in 6 min. The dots were not to touch the edges of the circles. The score was based on the number of correct responses.

Perceptual speed test (Gelfman et al., 1979). Using a set of numbers, the patient's task was to mark all the digits in a row which were identical with the one circled at the beginning of the row. The number of correct responses during a 2-min period was scored.

The three psychomotor paper-and-pencil tests were carried out before and 2 h after injection of the sedative.

Questionnaire

Each patient received a sealed envelope containing a questionnaire concerning the bronchoscopy and the patient's opinion of its acceptability (Korttila et al., 1978a). The questionnaire was completed the day after the procedure.

Data analysis

Statistical analysis of the data was carried out using the non-parametric Chi-squared test and Student's *t* test for independent means between the groups and for dependent means within the groups.

RESULTS

The principal differences recorded between diazepam and midazolam were that midazolam 0.1 mg kg^{-1} induced slightly more prolonged amnesia than diazepam 0.2 mg kg^{-1}, and that ability to walk was regained more slowly after midazolam 0.1 mg kg^{-1} than after diazepam 0.2 mg kg^{-1}

Cardiovascular effects and the performance of bronchoscopy

After each sedative regimen, both systolic and diastolic arterial pressures remained almost unaltered during bronchoscopy. They were slightly lower (always by less than 16 mm Hg systolic and 7 mm Hg diastolic) thereafter. Heart rates increased by an average of 10 beat min^{-1} after each of the sedatives.

The mean times (±SD) for performance of bronchoscopy varied according to the sedative used: diazepam 0.2 mg kg^{-1}, 8.3 ± 5.1 min; midazolam 0.05 mg kg^{-1}, 7.3 ± 4.0 min; midazolam 0.1 mg kg^{-1}, 9.3 ± 6.4 min.

Subjective assessments

The efficacy of local anaesthesia, patient co-operation and acceptability of the procedure to patients were similar in each experimental group (table II).

Amnesia

Amnesia to insertion and removal of the bronchoscope was significantly more common after diazepam 0.2 mg kg^{-1} ($P < 0.05$) and midazolam 0.1 mg kg^{-1} ($P < 0.01$) than after midazolam 0.05 mg kg^{-1} (table III). Two hours after injection, failure to recall removal of the bronchoscope was recorded for 70% of patients who received diazepam 0.2 mg kg^{-1}, 40% of those who received midazolam 0.05 mg kg^{-1} and 83% of those receiving midazolam 0.1 mg kg^{-1}. The amnesic action of midazolam 0.1 mg kg^{-1} lasted longer than that of diazepam 0.2 mg kg^{-1}. Twenty-three per cent of patients who received midazolam 0.1 mg kg^{-1} did not remember that Romberg's test had been performed at 30 min, when questioned 60 min after injection. Only 4% of patients receiving diazepam did not remember Romberg's test (table III).

Recovery

The patient's ability to stand steadily and walk along a straight line became normal significantly ($P < 0.05$ to $P < 0.01$) more slowly in those who received midazolam 0.1 mg kg^{-1} than in patients who received midazolam 0.05 mg kg^{-1} or diazepam (table IV). Thirty minutes after the injection, 56%,

TABLE II. *Efficacy of local anaesthesia and patient co-operation during bronchoscopy (0 = poor, 100 = good) and acceptability of procedure determined after 2 h (0 = unpleasant, 100 = pleasant). (Mean values ± SD)*

Treatment	Efficacy of local anaesthesia	Patient co-operation	Acceptability to patients
Diazepam 0.2 mg kg^{-1} ($n = 27$)	73 ± 22	77 ± 24	72 ± 31
Midazolam 0.05 mg kg^{-1} ($n = 25$)	72 ± 26	84 ± 18	70 ± 29
Midazolam 0.1 mg kg^{-1} ($n = 24$)	63 ± 28	76 ± 26	82 ± 22

TABLE III. *Amnesia for bronchoscopy and for recovery tests 2 h afterwards (% of total).* *P < 0.05 *and* **P < 0.01 v. *midazolam 0.05 mg kg*$^{-1}$

Treatment	Amnesia for bronchoscope		Failure to recall	
	Insertion	Removal	Standing test at 30 min	Walking test at 60 min
Diazepam 0.2 mg kg^{-1} ($n = 27$)	67*	70*	4	4
Midazolam 0.05 mg kg^{-1} ($n = 25$)	36	40	4	4
Midazolam 0.1 mg kg^{-1} ($n = 24$)	75**	83**	23	9

TABLE IV. *Percentage of patients who could not stand steadily or walk along a straight line 30, 60 and 120 min after injection of diazepam or midazolam.* $^*P < 0.05$ v. *midazolam 0.05 mg kg^{-1}*; $^{**}P < 0.01$ v. *diazepam and midazolam 0.05 mg kg^{-1}*; $^{***}P < 0.05$ v. *diazepam*

Treatment	Unable to stand steadily after 30 min	60 min	120 min	Unable to walk along a straight line after 30 min	60 min	120 min
Diazepam 0.2 mg kg^{-1} ($n = 27$)	56	7	0	63	22	0
Midazolam 0.05 mg kg^{-1} ($n = 25$)	32	16	0	56	20	4
Midazolam 0.1 mg kg^{-1} ($n = 24$)	67*	17	8	83*	58**	17***

TABLE V. *Recovery (visualization, aiming and perceptual speed tests). Mean values ± SD before sedation and 2 h afterwards*

Treatment	Visualization test, numbers correct: Before sedation	After 2 h	Aiming test, numbers correct: Before sedation	After 2 h	Perceptual speed test, numbers correct: Before sedation	After 2 h
Diazepam 0.2 mg kg^{-1}	9.5 ± 1.0	9.0 ± 1.8	231 ± 62	240 ± 66	15.3 ± 3.8	16.6 ± 4.3
Midazolam 0.05 mg kg^{-1}	9.1 ± 2.0	8.5 ± 2.2	207 ± 67	221 ± 71	13.9 ± 4.4	13.5 ± 4.3
Midazolam 0.1 mg kg^{-1}	9.0 ± 2.5	8.5 ± 2.8	223 ± 49	237 ± 61	15.4 ± 4.9	16.3 ± 6.0

32% and 67% of patients receiving diazepam 0.2 mg kg^{-1}, midazolam 0.05 mg kg^{-1} or midazolam 0.1 mg kg^{-1}, respectively, were unable to stand steadily. At 60 min, the corresponding figures for patients unable to walk along a straight line were 22%, 20% and 58%. All patients who had received diazepam were able to walk along a straight line 2 h after the injection, but 17% of patients receiving midazolam 0.1 mg kg^{-1} were unable to do so (table IV).

With the visualization, aiming and perceptual speed tests, there were no differences between patients of different sedative treatment groups (table V). Two hours after sedation, the patient's psychomotor performance in each test was similar to that measured before sedation.

Questionnaire

The acceptability of both sedation and the procedure were confirmed in each group (table VI). No retrograde amnesia was associated with diazepam or midazolam administration. On the day after diazepam 0.2 mg kg^{-1} and midazolam 0.1 mg kg^{-1}, only 22% and 8% of patients, respectively, remembered bronchoscopy having been performed. After midazolam 0.05 mg kg^{-1}, the figure was 52%.

TABLE VI. *Answers to the questionnaire (% of totals).* $^*P < 0.05$ *and* $^{**}P < 0.01$ v. *midazolam 0.05 mg kg^{-1}*

	Treatment: Diazepam 0.2 mg kg^{-1}	Midazolam 0.05 mg kg^{-1}	Midazolam 0.1 mg kg^{-1}
Remembered			
Local anaesthesia	100	100	100
Insertion of needle	100	96	92
Bronchoscopy	22*	52	8**
Would like next bronchoscopy performed similarly	85	72	88
Remembered			
Standing	89	96	83
Walking along line	96	96	92
Marking spots	100	100	92
Condition on the following afternoon			
Normal	26	40	38
Unusually tired	56	28	58
Sore throat	56	44	83

DISCUSSION

We wanted to assess midazolam as an i.v. sedative because findings during gastroscopy (Al-Khudhairi, Whitwam and McCloy, 1982; Brophy et al., 1982; Berggren et al., 1983; Bardhan et al., 1982) had indicated that midazolam might be preferable to diazepam for inducing mild sedation during short procedures.

The practice of early discharge of patients from hospital after outpatient procedures highlights the need to test for recovery after sedation. Both Romberg's test and the test of capacity to walk along a straight line are easy to perform, and are indices of the co-ordination skills which are affected to the greatest degree, and for the longest time, after sedation with benzodiazepines (Korttila and Linnoila, 1975, 1976; Korttila et al., 1978a). These tests obviously do not indicate "street-fitness" or full psychomotor recovery, but can help clinicians to reach a decision regarding the discharge of patients after sedation or anaesthesia (Korttila, 1981).

Visualization and aiming tests have been shown to be sensitive measures of mental function after cyclopropane anaesthesia (James, 1969) and flunitrazepam sedation (Korttila et al., 1978b). Scores in the perceptual speed test have been shown to be impaired after sedation with diazepam and i.v. anaesthetics (Gelfman et al., 1979; Korttila et al., 1981). We used these tests to study differences between recovery in various treatment groups, but found that, after midazolam, walking along a straight line was a more sensitive index of recovery than were these psychomotor tests.

Amnesia is less frequent to tactile stimuli than to events or visual stimuli following the administration of diazepam (Korttila, 1980a). Bronchoscopy is a frightening and powerful tactile stimulus, and is easy to remember, which may explain why we did not find the greater degree of amnesia following midazolam, compared with diazepam, observed by other investigators (Whitwam, Al-Khudhairi and McCloy, 1983; Dixon et al., 1984).

Our aim was to study doses of diazepam and midazolam which were similar in respect of amnesic action, and to compare side effects and recovery after such doses. Since the amnesia to bronchoscopy with diazepam 0.2 mg kg^{-1} proved similar in this study to that with midazolam 0.1 mg kg^{-1}, we considered comparison of rates of recovery after the two benzodiazepines at these doses to be justified.

Midazolam disappears from the blood much faster than diazepam. Its half-life (mean ±SD) during the elimination phase has been reported to be 2.4 ± 0.8 h (Allonen, Ziegler and Klotz, 1981) and 1.77 ± 0.83 h (Smith, Eadie and O'Rource-Brophy, 1981). That for diazepam is considerably longer (20–60 h) (Korttila, 1980b). However, recent clinical studies, and our results, suggest that the rapid disappearance of midazolam from the blood is not associated with rapid recovery. Dixon and others (1984) found no difference in the rate of recovery using the Trieger test in patients receiving midazolam 0.08 mg kg^{-1} or diazepam 0.15 mg kg^{-1} i.v. to supplement regional blocks. Whitwam, Al-Khudhairi and McCloy (1983) reported recovery as assessed by Romberg's test to be similar after midazolam and diazepam at doses comparable in potency, given for gastroscopy. Kawar and colleagues (1982), using a pegboard test, found a similar recovery time in patients receiving midazolam 0.1 mg kg^{-1} or diazepam 0.2 mg kg^{-1} i.v.as a sedative in dentistry.

Our finding that the ability of patients to stand steadily and walk along a straight line reverted to normal more slowly after midazolam 0.1 mg kg^{-1} than after diazepam 0.2 mg kg^{-1}, reflects the failure of Kawar and colleagues (1982), Whitwam, Al-Khudhairi and McCloy (1983), and Dixon and colleagues (1984) to demonstrate rapid recovery after midazolam, and suggests that testing the ability to walk along a straight line is a sensitive test for measuring the residual effects of midazolam. One explanation for the clinical finding that recovery from midazolam is not as fast as its pharmacokinetics would suggest, is that one metabolite of midazolam, α-hydroxymidazolam, has pharmacological activity. Crevoisier and others (1983) reported that α-hydroxymidazolam contributes to the central nervous system effects of midazolam, especially after oral administration.

Our conclusion is that, if doses of midazolam or diazepam, comparable in potency, are given during bronchoscopy, recovery of psychomotor function is not more rapid after sedation with midazolam than after sedation with diazepam.

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CARDIOVASCULAR EFFECTS OF A CHLORMETHIAZOLE INFUSION IN COMBINATION WITH EXTRADURAL ANAESTHESIA

C. J. SINCLAIR, D. FAGAN AND D. B. SCOTT

SUMMARY

The cardiovascular effects of an infusion of chlormethiazole 30–40 ml min^{-1} were studied in six patients following an extradural injection of 2% lignocaine. There were small but statistically significant decreases in mean arterial pressure and left ventricular ejection time during the infusion. Increases in the pre-ejection period were noted, but there were no significant changes in cardiac output, stroke volume or heart rate. Patient acceptance was high. It is concluded that sedation with an infusion of chlormethiazole, during surgery carried out under extradural anaesthesia, has no clinically adverse cardiovascular effects.

Although the use of chlormethiazole (CTZ) was considered inappropriate for the induction and maintenance of anaesthesia (Dundee, 1958) on account of the lack of analgesic activity, more recent reports (Schweitzer, 1978; Mather and Cousins, 1980) have suggested that it is a useful agent with which to provide sedation during surgery performed under regional anaesthesia. Previous studies of the cardiovascular effects of CTZ, both as sole agent in healthy volunteers (Wilson, Stephen and Scott, 1969) and in combination with nitrous oxide and pethidine in general anaesthesia (Christensen, Andreasen and Kristoffersen, 1983) have shown acceptable cardiovascular stability. However, while drugs producing marked sedation may have few adverse cardiovascular effects when given alone, this may not be so when they are combined with extradural anaesthesia, since the latter causes widespread sympathetic blockade. The present study was undertaken to assess the cardiovascular effects of CTZ when administered in association with extradural blockade.

PATIENTS AND METHODS

Six female patients scheduled for major gynaecological surgery, for which extradural anaesthesia was considered appropriate, agreed to take part in this study. No patient had a history of cardiac disease nor was any taking medication likely to affect the cardiovascular system. The nature of the study, which had approval from the local ethics committee, was explained and the patient's consent obtained.

One hour before the start of the study, five patients received diamorphine 5 mg and atropine 0.6 mg, and one patient (aged 67 yr) received diamorphine 2.5 mg and atropine 0.6 mg i.m. An extradural catheter was inserted at the L3–4 intervertebral space. Cardiovascular variables were monitored non-invasively using a Minnesota Impedence Cardiograph (Model 304 A) coupled with a Bell and Howell oscillograph (Model 5–137) and Dynamap 840 arterial pressure monitor. Mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), stroke volume (SV), left ventricular ejection time (LVET) and pre-ejection period (PEP) were calculated. The resistivity of blood was calculated from the patient's haematocrit using the formula $\rho = 2.102\ \text{Hct} + 30.098$ (Hill and Thomson, 1975).

With the patient lying supine and comfortable, three sets of recordings were obtained at intervals of 2 min to obtain control data. Sixteen to eighteen millilitre of 2% lignocaine was injected via the extradural catheter and further sets of recordings obtained at 2, 4, 6 and 8 min following injection. At this point, a rapid infusion of 0.8% CTZ (30–40 ml min^{-1} i.v.) was given until the patient became unconscious. The infusion rate was then adjusted to

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maintain sedation of such a degree that the patients were either quite unresponsive or virtually so. Four further sets of measurements were obtained at 2, 4, 6 and 8 min from the start of the chlormethiazole infusion. Following the final series of measurements, patients were prepared for surgery, and the chlormethiazole infusion continued to provide adequate sedation during the operation.

Statistical analysis of the data was performed using Wilcoxon's matched pair signed rank test, $P < 0.05$ being taken to indicate statistical significance.

RESULTS

All patients underwent major vaginal surgery and the combination of extradural analgesia and sedation with CTZ proved satisfactory in all. The ages of the patients ranged from 33 to 67 yr (mean 51 yr), their weights from 54.0 to 89.9 kg (mean 65.6 kg) and their heights from 152.4 to 165.1 cm (mean 159.6 cm).

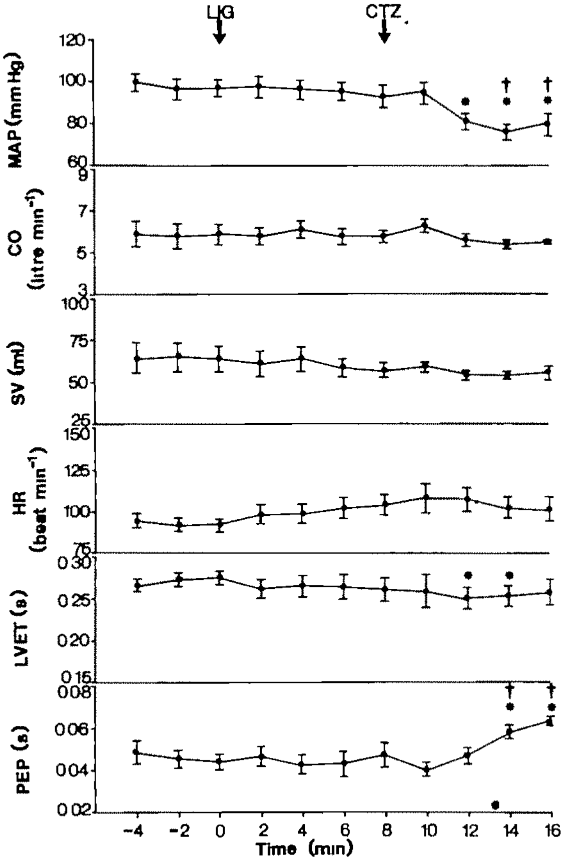

FIG 1. Mean (± SEM) MAP, CO, SV, HR, LVET and PEP *v.* time. LIG = extradural injection of lignocaine; CTZ = start of chlormethiazole infusion. Statistical significance ($P < 0.05$): *control mean compared with chlormethiazole infusion; †8 min after extradural injection compared with chlormethiazole infusion.

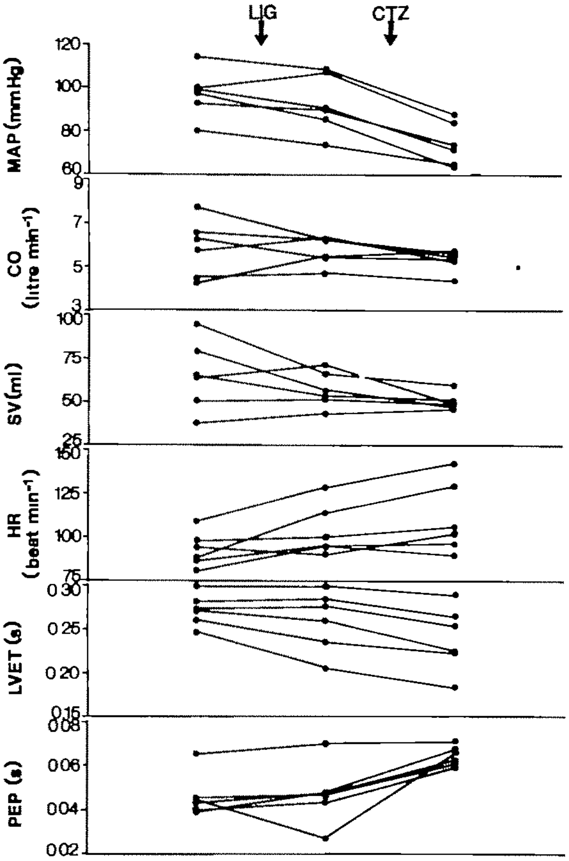

FIG. 2. Results in individual patients of mean control values, values 8 min after extradural injection, and lowest MAP, CO, SV, LVET and highest HR and PEP during the chlormethiazole infusion, these being considered the least desirable changes caused by CTZ.

Deep sedation was produced following the rapid infusion of 0.8% CTZ approximately 70–100 ml and the mean total CTZ infused over the 8 min of the study was 190 ml (range 125–220 ml).

Cardiovascular variables

Mean data (± SEM) for each set of recordings are displayed in figure 1. Figure 2 shows the mean control values from each patient, the values 8 min following the extradural injection, and the lowest mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV), left ventricular ejection time (LVET), highest heart rate (HR) and pre-ejection period (PEP) without regard to time during the CTZ infusion. It was assumed that these were the least desirable cardiovascular effects.

Mean arterial pressure. There were small but statistically significant decreases in MAP at 4, 6 and 8 min after the start of the CTZ infusion when compared with control values, and at 6 and 8 min following the start of the CTZ infusion when compared with values immediately before the start of the infusion (8 min after extradural injection). The lowest arterial pressure recorded during the study period was 89/53 mm Hg.

Cardiac output. Cardiac output was relatively constant during the study period.

Stroke volume. There was a small but insignificant decrease in stroke volume which was associated with an increase in heart rate. This was noted initially during the period following the extradural injection but continued during the CTZ infusion.

Heart rate. Although there were no statistically significant differences recorded in heart rate, there was a tendency for the heart rate to increase during the period following the extradural injection and then to remain fairly constant during the CTZ infusion. Two patients had tachycardia with heart rates of 142 and 128 beat min^{-1} immediately following the start of the CTZ infusion but, during the second 4 min of the CTZ infusion, their heart rates decreased to values similar to those immediately preceding the infusion.

Systolic time indices. There were small but statistically significant decreases in LVET 4 and 6 min after the start of the CTZ infusion when compared with control values. Similarly, there were small but statistically significant increases in PEP 6 and 8 min after the start of the infusion when compared with control and pre-infusion data.

DISCUSSION

Before this study, it had been our clinical impression that the combination of extradural blockade and sedation with a CTZ infusion produced haemodynamically stable conditions. Schweitzer (1978), and Mather and Cousins (1980) have also commented on this, but no study of the detailed cardiovascular effects of the combination has been published. Although starting the infusion of CTZ before the extradural puncture has been suggested by Seow and colleagues (1981)—to make the procedure more comfortable for patients—it has been our practice to perform the extradural puncture first in the awake, co-operative patient. By doing so in this study, we were able to study the effects of CTZ in patients who had some degree of sympathetic blockade and were arguably more vulnerable to any adverse cardiovascular effect.

The initial rate of infusion (30–40 ml min^{-1}) was fast and rapidly produced loss of consciousness. In a previous study of the cardiovascular effects of CTZ in healthy volunteers Wilson, Stephen and Scott (1969) used 12–20 ml min^{-1}. However, the initial infusion rate used in this study is the more common in clinical use and would be expected to show any deleterious cardiovascular effects, if they existed.

Although there were statistically significant decreases in arterial pressure, the lowest value recorded was 89/53 mm Hg. No fluids were infused i.v. during the study period except 0.8% CTZ, and no patient required a vasopressor. A decrease in arterial pressure of this degree is common during extradural anaesthesia, and it is interesting to note that Seow and colleagues (1981) noticed an increase of 27% in systolic arterial pressure during the first few minutes of chlormethiazole infusion in healthy volunteers. Cardiac output and stroke volume were stable during the trial period. Two of our patients experienced transient increases in heart rate at the start of the infusion, but these settled within a few minutes. This contrasts with studies in healthy volunteers, in whom Wilson, Stephen and Scott (1969) noticed an average increase of 48.7% and Seow and co-workers (1981) recorded an increase of 50% over resting heart rate, and it was for this reason that CTZ infusion was suggested as a supplement to extradural anaesthesia. Certainly, none of our patients experienced a bradycardia: the slowest heart rate recorded was 83 beat min^{-1}. The small, but statistically significant, changes in systolic time indices had no noticeable effect on cardiac output. Christensen, Andreasen and Kristoffersen (1983) noticed similar changes in systolic time indices when CTZ was infused during general anaesthesia, but these changes were much smaller than during a thiopentone infusion.

Patient acceptance of this method of anaesthesia was high in this study.

Patients awoke rapidly when the infusion was stopped at the end of their operation. Seow, Mather and Roberts (1981), studying the pharmacokinetics and pharmacodynamics of CTZ, came to the conclusion that it was a good choice for i.v. sedation because of its rapid clearance and short elimination half-life. In that study, psychometric testing was carried out and showed a return to normal within 30 min of cessation of the infusion in heavily sedated volunteers. We believe that the properties of rapid awakening and cardiovascular stability support the use of an infusion of chlormethiazole to produce sedation during surgical procedures carried out under extradural blockade.

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EFFECT OF ALFENTANIL ANAESTHESIA ON THE ADRENOCORTICAL AND HYPERGLYCAEMIC RESPONSE TO ABDOMINAL SURGERY

I. W. MØLLER, T. KRANTZ, E. WANDALL AND H. KEHLET

SUMMARY

Plasma concentrations of cortisol and glucose were measured from before to 9 h after skin incision in 24 patients undergoing abdominal hysterectomy. The patients were randomly allocated to receive either high-dose alfentanil anaesthesia (150 $\mu g\ kg^{-1}$ initially, followed by continuous infusion at a rate of 3 $\mu g\ kg^{-1}\ min^{-1}$) or neurolept anaesthesia (droperidol 0.25 mg kg^{-1} plus fentanyl 5 $\mu g\ kg^{-1}$ initially, followed by intermittent incremental doses of fentanyl 50 μg). The intraoperative and initial postoperative increases in plasma cortisol and glucose concentrations were inhibited ($P < 0.05$) by alfentanil but, later in the postoperative period, both groups showed identical increases in cortisol and glucose concentrations. Mean arterial pressure and heart rate were more stable in the alfentanil group. The concept of "stress-free" anaesthesia during high-dose opiate administration seems to be valid during operation and for the initial 1–3 h into the postoperative period.

High-dose opiate anaesthesia with morphine, fentanyl, alfentanil or sufentanil initially inhibits the intraoperative endocrine-metabolic response to open heart surgery (George et al., 1974; Stanley et al., 1979; Sebel et al., 1981; de Lange et al., 1982; 1983; Bovill et al., 1983). However, in all these studies, the opiate-induced suppression of the endocrine and metabolic indices was reversed on the commencement of the bypass. Accordingly, no prolonged metabolic effect could be demonstrated following high-dose opiate anaesthesia in patients undergoing open-heart surgery (Brandt et al., 1978; Walsh et al., 1981). Nevertheless, the concept of stress-free anaesthesia associated with the use of high-dose opiates has gained much popularity, despite the fact that no controlled clinical study has demonstrated a beneficial effect on postoperative morbidity.

High-dose opiate anaesthesia can also inhibit the endocrine-metabolic response to intra-abdominal surgery (Hall et al., 1978; Cooper et al., 1981; Haxholdt, Kehlet and Dyrberg, 1981), but no information is available on the effect on metabolic changes after operation. The purpose of our study was to investigate the influence of high-dose alfentanil anaesthesia on the intra- and postoperative adrenocortical and hyperglycaemic responses to abdominal hysterectomy.

PATIENTS AND METHODS

Twenty-four otherwise healthy, premenopausal women scheduled for elective abdominal hysterectomy were randomly allocated to receive either high-dose alfentanil anaesthesia (group I) or neurolept anaesthesia (group II). None of the patients was suffering from hormonal diseases or had received any medication, including hormonal contraceptives. The durations of surgery (108 ± 6 min (group I), 95 ± 9 min (group II) (mean ± SEM)) were not different ($P > 0.05$) between the two groups; mean age was slightly higher in the neurolept group (41 ± 1 yr *v.* 35 ± 1 yr, $P < 0.05$). All patients gave written informed consent to the study.

The patients were premedicated with pethidine 1 mg kg^{-1} 1 h before the induction of anaesthesia. All operations began between 8 a.m. and 1 p.m. After atropine 0.5 mg and gallamine 20 mg i.v.,

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group I received alfentanil 150 μg kg^{-1} for the induction of anaesthesia, followed by a continuous infusion of alfentanil 3 μg kg^{-1} min^{-1} until 5 min before the end of surgery. In group II, anaesthesia was induced with droperidol 0.25 mg kg^{-1} and fentanyl 5 μg kg^{-1}, followed by incremental doses of fentanyl 50 μg throughout operation (total dose of fentanyl 0.42 ± 0.02mg). In both groups a small dose of thiopentone was administered before intubation, if the patients were conscious. Orotracheal intubation was facilitated by suxamethonium 1–1.5 mg kg^{-1} and gallamine was administered to provide muscular relaxation during the surgical procedure. Pulmonary ventilation was controlled manually via a circle system using 67% nitrous oxide in oxygen. The patients received isotonic saline 10–15 ml kg^{-1} h^{-1} i.v. during the first 2 h and thereafter 1–2 ml kg^{-1} h^{-1}. Intraoperative bleeding, which never exceeded 500 ml (372 ± 51 ml (group I), 392 ± 47 ml (group II)), was not different between the two groups ($P > 0.05$), and was replaced with isotonic saline 2.5 ml/ml blood. None of the patients received blood transfusion or sympathomimetic drugs.

Venous blood was drawn for the measurement of cortisol and glucose concentrations 30 and 15 min before the induction of anaesthesia, at skin incision and again 0.5, 1, 2, 3, 4, 6 and 9 h later. Plasma cortisol concentration was measured by a competitive protein-binding technique (Kehlet, Binder and Engbæk, 1974) and plasma glucose concentration by a routine oxidase method. ECG and heart rate were displayed continuously on an oscilloscope, and arterial pressure was monitored intermittently by sphygmomanometry.

Statistical analysis was performed using the Wilcoxon test for intragroup variation and the Mann–Whitney test for intergroup variation. Probability values less than 0.05 were regarded as significant.

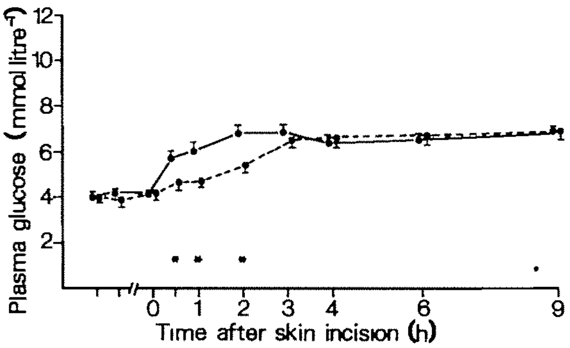

FIG 2 Changes in plasma glucose concentration (mean ± SEM) during and after abdominal hysterectomy under high-dose alfentanil anaesthesia (●—●) ($n = 12$) or neurolept anaesthesia (●—●)($n = 12$). $*P < 0.02$.

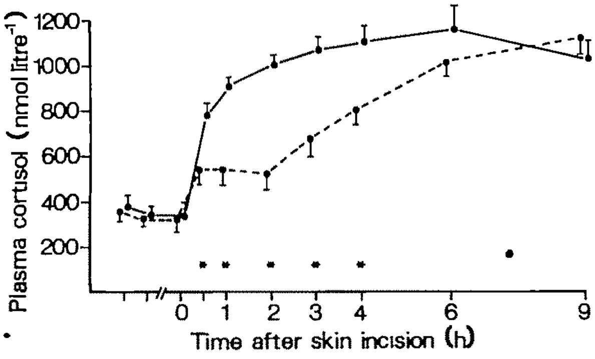

FIG. 1. Changes in plasma cortisol concentration (mean ± SEM) during and after abdominal hysterectomy under high-dose alfentanil anaesthesia (●—●) ($n = 12$) or neurolept anaesthesia (●—●) ($n = 12$). $*P < 0.01$.

RESULTS

Plasma cortisol concentration (fig. 1)

In both groups, plasma cortisol concentration increased significantly 30 min after skin incision and remained increased throughout the study. The plasma concentrations of cortisol in the alfentanil group were significantly lower, from 30 min to 4 h after skin incision, than those in the neurolept group. From 6 h and onwards, the concentrations were similar in the two groups.

Plasma glucose concentration (fig. 2)

In both groups, plasma glucose concentration increased significantly 30 min after skin incision and remained increased throughout the study. Com-

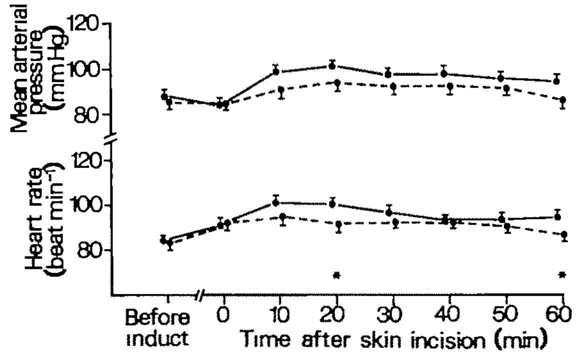

FIG 3. Mean changes (± SEM) in mean arterial pressure and heart rate during and after abdominal hysterectomy under high-dose alfentanil anaesthesia (●—●)($n = 12$) or neurolept anaesthesia (●—●) ($n = 12$). $*P < 0.05$.

pared with the neurolept group, plasma glucose concentrations were significantly lower in the alfentanil group from 30 min to 2 h after skin incision; the concentrations were similar from 3 h and onwards in both groups.

Haemodynamic indices (fig. 3)

There were no significant differences in mean arterial pressure between the alfentanil and neurolept groups during the first 60 min of surgery. Mean arterial pressure was increased significantly throughout the study in the neurolept group, and at 10, 20, 30 and 40 min after skin incision in the alfentanil group when compared with the average value recorded in the interval from before induction to before skin incision. In the patients receiving alfentanil anaesthesia, the heart rate was lower ($P < 0.05$) 20 and 60 min after the start of surgery when compared with the neurolept group. Mean heart rate had increased significantly 10 and 20 min after skin incision when compared with the average value obtained between preinduction and before skin incision in the neurolept group; no significant changes were observed in the alfentanil group.

Side effects

Vomiting occurred in three patients receiving alfentanil. Prolonged recovery with severe respiratory depression necessitating reversal with naloxone occurred in three patients in the alfentanil group. Neither vomiting nor respiratory depression was seen in the patients receiving neurolept anaesthesia.

DISCUSSION

This study demonstrated that alfentanil anaesthesia suppresses the changes in the plasma concentrations of cortisol and glucose during surgery, thus substantiating the studies performed during open heart surgery under high-dose opiate anaesthesia with morphine, fentanyl, alfentanil or sufentanil (George et al., 1974; Brandt et al., 1978; Stanley et al., 1979; Sebel et al., 1981; Walsh et al., 1981; de Lange et al., 1982, 1983; Bovill et al., 1983). In most of these studies the by-pass procedure, which apparently represents a major stimulus, led to an inhibition of the suppressant effect of the high-dose opiate anaesthesia on the stress response and no effect on endocrine-metabolic changes could be demonstrated in the period after operation (Brandt et al., 1978; Walsh et al., 1981). Studies in other procedures without cardiopulmonary by-pass have not included measurements beyond the 2–3 h after administration of a single high dose of fentanyl (Hall et al., 1978; Cooper et al., 1981; Haxholdt, Kehlet and Dyrberg, 1981), and it is not known whether an initial inhibition of the stress response by a high-dose opiate anaesthetic regimen has a prolonged effect on endocrine-metabolic variables after such procedures. Our results demonstrate clearly that the intraoperative blockade of the stress response by the continuous administration of high-dose opiate anaesthesia using a short-acting drug like alfentanil has no effect on endocrine-metabolic changes beyond 1–3 h after the completion of the administration of the drug. These results accord with studies using single-dose spinal anaesthesia (Møller et al., 1984) or extradural analgesia with local anaesthetics (Lush et al., 1972), both of which block the afferent neurogenic pathways from the surgical area and, thereby, the stress response during surgery. However, in both studies the regression of sensory analgesia led to the endocrine-metabolic variables reaching values comparable to those observed in patients 1–3 h following general anaesthesia.

In accord with others (de Lange et al., 1982, 1983); we found that alfentanil anaesthesia using high doses led to greater stability of arterial pressure and heart rate during surgery. However, the frequency of respiratory depression after operation was unacceptable, and with the high frequency of nausea and vomiting make continuous high-dose alfentanil anaesthesia unsuitable for surgical procedures of intermediate duration.

In conclusion, the concept of "stress-free" anaesthesia using high-dose opiate anaesthesia seems valid only for the intraoperative period and the first 1–3 h in the postoperative period. Based upon the hypothesis that blockade of surgically-induced metabolic changes will lessen postoperative complications (Kehlet, 1982), it is questionable if high-dose opiate anaesthesia will lead to a reduction in postoperative morbidity, since the endocrine-metabolic response to surgery is most pronounced in the period after operation.

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CONTINUOUS MONITORING OF BLOOD GLUCOSE CONCENTRATION DURING OPEN-HEART SURGERY

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SUMMARY

Continuous monitoring of blood glucose concentration was compared with frequent intermittent sampling in 12 non-diabetic adult patients undergoing open-heart surgery with cardiopulmonary by-pass using priming fluids free of glucose. Continuous monitoring revealed several changes which were not detected on intermittent sampling. Blood glucose concentration decreased by 2 mmol litre^{-1} ± 0.5 (SEM) ($P < 0.01$) immediately on the institution of CPB, and increased during the succeeding minutes. Rewarming from hypothermic by-pass was associated with a 3 (± 0.5)-mmol litre^{-1} increase in blood glucose concentration ($P < 0.01$). Commencement of infusions of sympathomimetic agents resulted in a similar increase.

Intermittent sampling has formed the basis of previously published reports on the changes in blood glucose concentration during open-heart surgery, and many workers have demonstrated marked alterations in glucose concentration under these circumstances (Moffitt et al., 1970, 1971; Allison, 1971; MacDonald et al., 1975; Yokota et al., 1977; Brandt et al., 1978; Landymore, Murphy and Kinley, 1981; Walsh et al., 1981). However, recent work from groups studying the management of diabetes during open-heart surgery has suggested that intermittent sampling, even of the frequency suggested by Yokota and colleagues (1977), may fail to reveal the true magnitude, rapidity or even occurrence of some of the changes in blood glucose concentration (Kuntschen, Galletti and Hahn, 1981; Elliott et al., 1984). It is not known whether similar changes occur in non-diabetic patients undergoing open-heart surgery. To determine this, we have compared intermittent with continuous monitoring of blood glucose concentration in 12 non-diabetic adult patients undergoing open-heart surgery.

PATIENTS AND METHODS

Patients, anaesthesia and cardiopulmonary bypass

Twelve adult patients undergoing elective open-heart surgery for valvular disease, and taken sequentially from the waiting list of one cardiac surgeon (M.P.H.), were studied. Written, informed consent was obtained from the patients. The programme of the investigation was approved by the Newcastle Health Authority Ethical Committee.

The following categories of patient were excluded from the study:

(i) Patients with known ischaemic heart disease.
(ii) Patients taking β-adrenoceptor blocking agents.
(iii) Patients with known endocrine or metabolic disorders, or an abnormal oral glucose tolerance test on admission.
(iv) Patients with known hepatic or renal disease.

To study the changes in blood glucose concentration which occurred during open-heart surgery and cardiopulmonary by-pass, it was felt that a pump prime free from glucose should be used, since glucose-containing primes result in large increases in blood glucose concentration which might mask lesser variations attributable to the technique itself (Elliott, 1983). Two such non-glucose primes are in use in the United Kingdom (all U.K. centres having

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been questioned): Hartmann's solution and Plasmalyte 148 (Travenol). Since Hartmann's solution contains lactate 29 mmol litre^{-1}, and lactate, at least in diabetic patients, has been shown to be gluconeogenic when infused during surgery (Thomas and Alberti, 1978), it was felt that the glucose concentrations should be monitored in association with the use of both primes. Thus, the 12 patients were randomly allocated to one of two groups:

Group 1: Six patients undergoing cardiopulmonary by-pass with a pump prime of Hartmann's solution.
Group 2: Six patients undergoing cardiopulmonary by-pass with a Plasmalyte 148 pump prime.

TABLE I. *Clinical details of the patients studied (mean values±SEM where applicable). AV = Aortic valve replacement; MV = mitral valve replacement; DV = double valve replacement*

	Prime	
	Hartmann's Solution (group 1)	Plasmalyte 148 (group 2)
Number	6	6
Age (yr)	59.8±3.3	56±1.7
Sex	2M, 4F	4M, 2F
Height (m)	1.59±0.02	1.71±0.02
Weight (kg)	60.1±1.1	67±4.6
Surface area (m^2)	1.63±0.02	1.77±0.07
Operation	MV, MV, MV MV, AV, DV	MV, AV, MV MV, MV, MV

TABLE II. *Composition (mmol litre^{-1}) of the by-pass pump priming fluid used in each group*

	Group 1 Hartmann's Solution	Group 2 Plasmalyte 148
Na^+	131	140
K^+	5	5
Ca^{2+}	2	5
Mg^{2+}	—	1.5
Cl^-	111	80
Lactate	29	—
Acetate	—	27

Clinical details of the patients are given in table I, and details of the two priming fluids in table II. The anaesthetic technique was as follows: premedication consisted of papaveretum 11.75 mg m^{-2} and hyoscine 0.25 mg m^{-2} i.m. 1 h before surgery. Anaesthesia was induced with thiopentone 120 mg m^{-2}, droperidol 11.75 mg m^{-2} and phenoperidine 2.4 mg m^{-2} i.v., and neuromuscular blockade produced by pancuronium 4.7 mg m^{-2}. Anaesthesia was maintained with nitrous oxide in oxygen plus intermittent injections of phenoperidine. Further pancuronium was added as required to permit intermittent positive pressure ventilation.

The perfusion technique was standardized: cardiopulmonary by-pass was conducted at 28 °C (veno–arterial cooling) at a flow of 2.4 litre m^{-2} min^{-1}, maintained at all temperatures. A Travenol membrane oxygenator was used in each patient, and pulsatile flow was utilized. Pulsatile flow was generated using a Stöckert (Stöckert Instrumente, München, F.R.G.) pulsatile roller-pump system set to deliver for 50% of the cycle at 90 beat min^{-1} whenever the left ventricle was not ejecting blood to the aorta. The prime volume of the system was 2.5 litre. No glucose-containing fluids were infused or used to flush the pressure monitoring systems. All the operations were performed by the same surgeon (M.P.H.). Cardioplegic arrest was achieved using a modified Kirklin solution at 4 °C and all excised valves were replaced with Ionescu–Shiley bovine xenografts.

Blood glucose sampling

The Biostator (Miles Laboratories Ltd, Stoke Poges, England) glucose-controlled insulin infusion system, shown in diagram form in figure 1, was used to estimate the blood glucose concentration continuously. From an indwelling double-lumen peripheral venous cannula, a small amount of blood (2 ml h^{-1}) was withdrawn continuously and, after dilution, passed across a glucose sensor (glucose oxidase membrane and polarographic electrode). The blood glucose concentration was relayed to a computer, allowing display and recording of the data. Intermit-

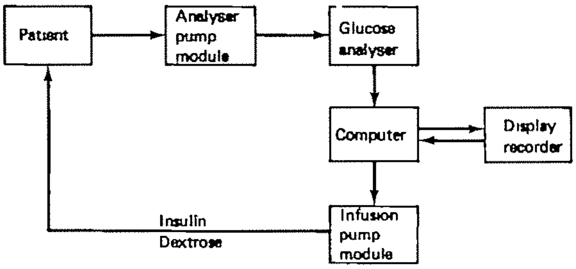

FIG. 1. Block diagram of the Biostator glucose-controlled insulin infusion system. The monitoring ability only was used in this study.

tent sampling of venous blood was carried out according to the sampling regimen shown in table III. Samples were drawn into fluorinated tubes and analysed using a sensitive fluorimetric assay.

Statistics

Student's *t* test, paired and unpaired, was used to evaluate the significance of differences within and between groups, respectively. Results are expressed as mean ± SEM.

RESULTS

Intermittent sampling

The results of blood glucose estimations obtained by intermittent sampling are shown in figure 2. There were no significant differences between groups 1 and 2 at any stage. Thus, these results may be conveniently described together.

There were no significant changes in blood glucose concentration before, or on institution of, cardiopulmonary by-pass. Blood glucose concentrations increased steadily from 5.6 ± 0.4 mmol litre^{-1} 5 min after the institution of by-pass to 10 ± 0.6 mmol litre^{-1} 5 min before the end of by-pass. There were no significant changes in blood glucose concentration on the cessation of by-pass, nor were there any significant decreases until the morning of the first day after operation when the mean glucose values were 8.4 ± 0.7. mmol litre^{-1}.

Continuous sampling

Because of a variable time-base, the data obtained from continuous monitoring do not lend themselves to cumulative graphical presentation. Thus, figures 3 and 4 are representative Biostator records from two patients. When analysed in relation to peri-operative events rather than to time, no significant differences in blood glucose concentration could be demonstrated between the two groups at any stage.

Following skin incision and before cardiopulmonary by-pass, there was a steady increase in blood glucose concentration of 1.3 ± 0.3 mmol litre^{-1} ($P < 0.01$). The institution of cardiopulmonary by-pass was associated with an abrupt decrease in blood glucose concentration of 2 ± 0.5 mmol litre^{-1} as the patient's blood was diluted by the prime. This was

TABLE III. *Regimen for intermittent sampling of venous blood*

Sample No.	Day	Time of event
1	1 Day before operation	08.00h
2		18.00h
3	Day of operation	08.00h
4		5 min After induction of anaesthesia
5		5 min After skin incision
6		5 min After heparin
7		5 min After onset of CPB
8		15 min
9		30 min
10		60 min
11		5 min Before end of CPB
12		5 min After protamine
13		1h After operation
14		2h
15		4h
16		6h
17		8h
18	1 Day after operation	08.00h
19		12.00h
20		18.00h
21	2 Days after operation	08.00h
22		18.00h
23	3 Days after operation	08.00h
24		18.00h
25	4 Days after operation	08.00h
26		18.00h
27	7 Days after operation	08.00h

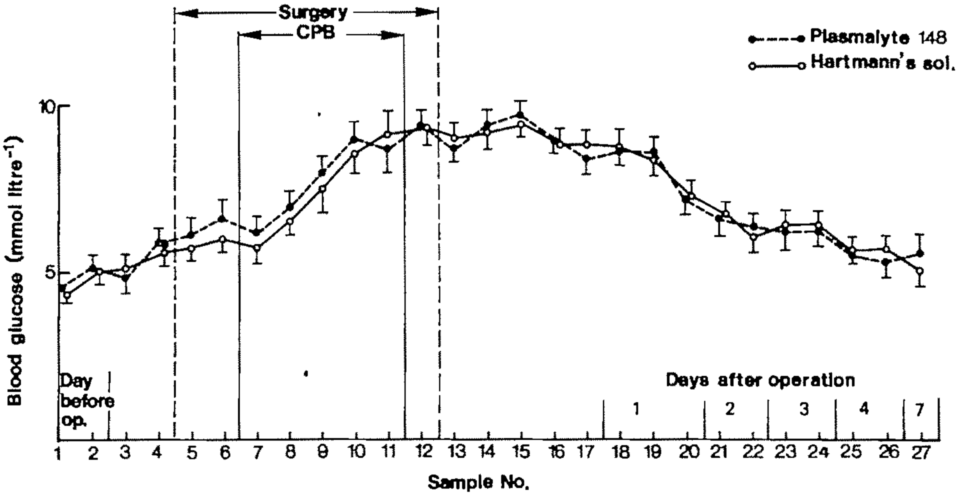

FIG. 2. Blood glucose concentrations in both groups as estimated by intermittent sampling.

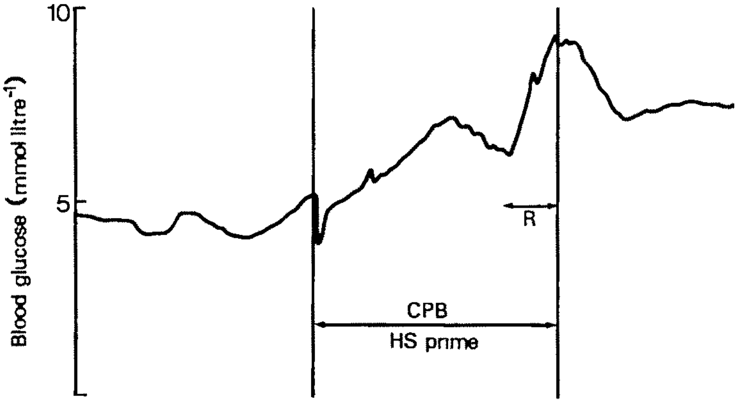

FIG. 3. Continuously monitored blood glucose concentration in a patient from group 1 (Hartmann's Solution prime) (HS prime). CPB = pulsatile CPB (28 °C); R = rewarming.

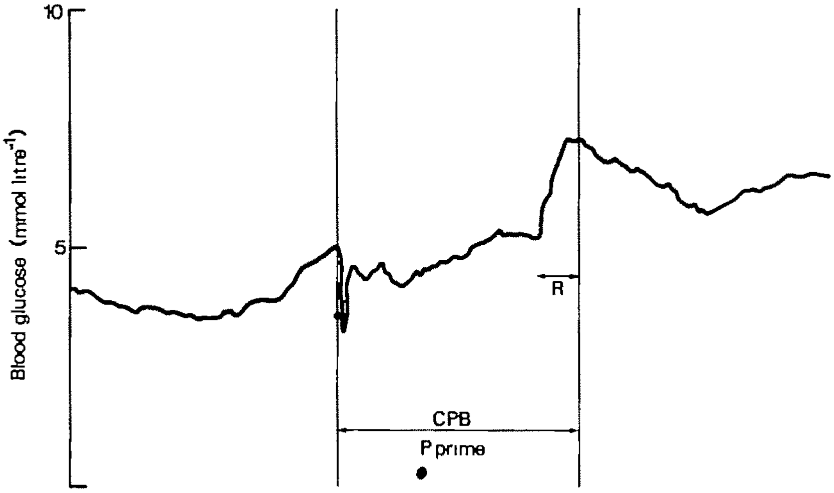

FIG 4. Continuously monitored blood glucose concentration in a patient from group 2 (Plasmalyte 148 prime) (P prime). CPB = pulsatile CPB (28 °C); R = rewarming.

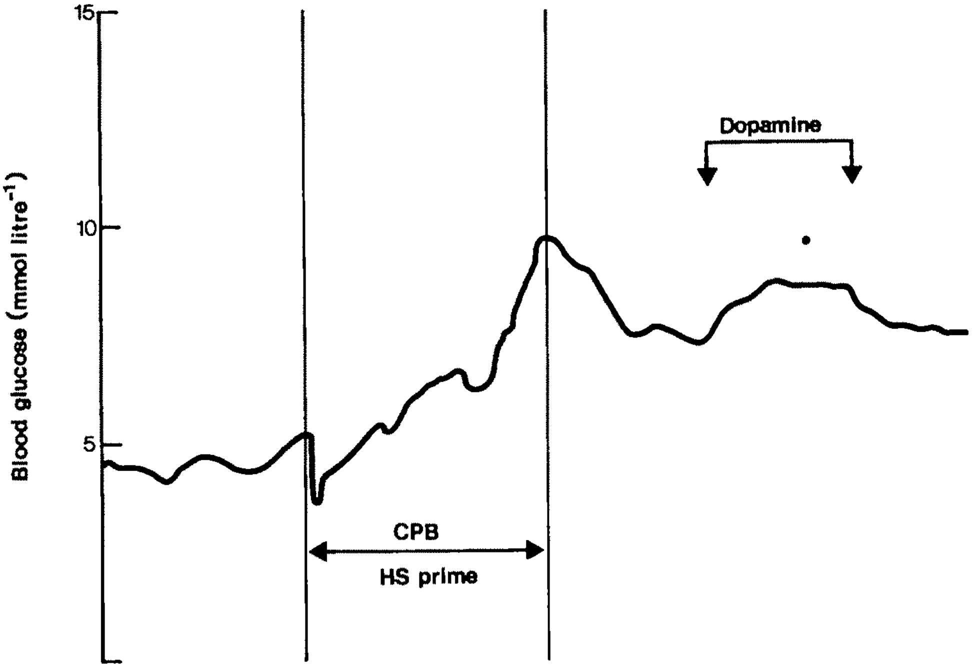

FIG 5. Continuously monitored blood glucose concentration showing the effect of an infusion of dopamine. CPB = pulsatile CPB (28 °C); HS prime = Hartmann's Solution prime.

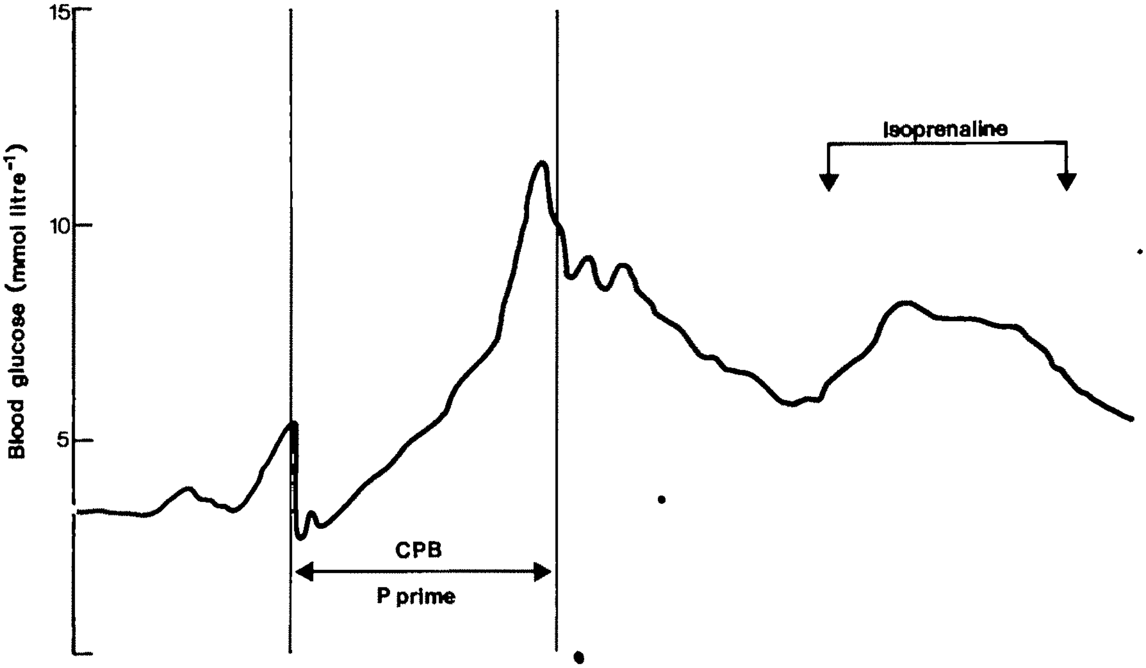

FIG 6. Continuously monitored blood glucose concentration showing the effect of an infusion of isoprenaline. CPB = pulsatile CPB (28 °C); P prime = Plasmalyte 148 prime.

followed by an increase to 9 ± 0.8 mmol litre^{-1} during the first hour of hypothermic by-pass. During rewarming, a much more rapid increase in blood glucose concentration was observed in all patients. This increase of 3 ± 0.5 mmol litre^{-1} was not demonstrated by intermittent sampling.

Thereafter, the blood glucose concentrations decreased to a mean of 9.5 + 0.8 mmol litre^{-1}, which had not varied significantly by 4 h into the postoperative period, when continuous monitoring was discontinued. Figures 5 and 6 demonstrate the effects on blood glucose concentration of the infusion of sympathomimetic agents. Four of the 12 patients required inotropic support at some stage in the period after operation. This was associated, in each case, with an increase in blood glucose concentration with a mean value of 2.5 + 0.4 mmol litre^{-1} which was sustained for the duration of the infusion —although the infusions were of fairly short duration (1.5–2.5 h). It should be noted that a variable and unpredictable increase in blood glucose concentration was observed during the rapid infusion of Citrate–Phosphate–Dextrose blood in those patients who received it, the increase being related to the glucose content of the transfused blood.

DISCUSSION

Previous reports using intermittent sampling of blood contain results similar to those obtained with intermittent sampling in this study, when similar primes were used. However, our comparison of continuous with intermittent sampling has shown that intermittent sampling failed to reveal several significant changes in blood glucose concentration. The decrease in blood glucose concentration on commencement of cardiopulmonary by-pass and the increases associated with rewarming and the infusion of sympathomimetic agents were not detected by intermittent sampling.

The decrease in blood glucose concentration (of 2 mmol litre^{-1}) with the onset of cardiopulmonary by-pass may be explained by dilution of the patient's circulating blood volume with the glucose-free pump prime. Some subsequent redistribution must occur as the prime equilibrates with the extracellular fluid. Thereafter, the steady increase in blood glucose concentration observed during the first hour of hypothermic cardiopulmonary by-pass merits consideration. High concentrations of catecholamines, particularly noradrenaline, are known to occur during hypothermic by-pass (Landymore et al., 1979; Stanley et al., 1980). Catecholamines are known to stimulate glycogenolysis and hepatic gluconeogenesis (De Fronzo, Sherwin and Felig, 1980). Thus, it is to be expected that there would be an increase in the release of glucose from the liver. In addition, the peripheral utilization of glucose is decreased greatly at these body temperatures (Black, Van Devanter and Cohn, 1976; Stoner et al., 1980), and this would account for the increase in blood glucose concentration observed during the first hour of by-pass. The changes in blood glucose concentration noted during rewarming are of interest also. During the rewarming phase, there may be changes in the blood concentrations of various hormones which are known to have profound effects on glucose metabolism. Thus, the concentrations of adrenaline and noradrenaline have been shown to increase considerably during the return to normothermia (Stanley et al., 1980; Landymore, Murphy and Kinley, 1981). This additional increase in catecholamine concentrations is likely to increase further the rates of hepatic and renal medulla glycogenolysis and gluconeogenesis, resulting in increased glucose release. In addition, the serum cortisol concentration increases during cardiopulmonary by-pass (Walsh et al., 1981) and the increased concentration has a synergistic effect with catecholamines on gluconeogenesis (De Fronzo, Sherwin and Felig, 1980). A direct stimulatory effect of increasing temperature on the enzyme systems involved in glucose production cannot be ruled out.

It is surprising that the increase in blood glucose concentration associated with rewarming occurs at a time when serum insulin concentrations have been shown to increase markedly. Insulin secretion is decreased during hypothermic cardiopulmonary by-pass, but increases rapidly during rewarming (Allison, 1971; Elliott, 1983). The relationship between the time course of the action of insulin on glucose uptake and utilization, and that attributable to endocrine stimulation of glucose production during rewarming has not been established by us.

The increases in blood glucose concentration observed during the infusions of sympathomimetic agents are presumably the result of direct stimultion of glycogenolysis and gluconeogenesis, and of the indirect effect of increasing insulin resistance. The increases in blood glucose concentration observed during the infusions of blood almost certainly resulted from the glucose content of the transfusion. C–P–D blood contains from 7 to 22 mmol litre^{-1} of glucose (mean 19 mmol litre^{-1}). Further clarification of these glucose fluxes would require catheterization or turnover studies.

We did not observe a gluconeogenic effect of the lactate primes in these non-diabetic patients undergoing open-heart surgery with hypothermic bypass, there being no differences in the blood glucose concentrations between the groups at any stage. However, the patient population and intraoperative management were quite different from those reported by Thomas and Alberti (1978), who demonstrated a gluconeogenic effect of lactate infusions in diabetic patients undergoing surgery.

Apart from the obvious pathophysiological interest of these results, the consequent increase in understanding of blood glucose homeostasis during open-heart surgery is of importance in clinical management. This will be particularly true of the patient with diabetes. Indeed, both we (Elliott et al., 1984) and others (Kuntschen, Galletti and Hahn, 1981) have observed similar changes in diabetic patients undergoing open-heart surgery using the Biostator blood glucose control.

It is clear from this study that the continuous monitoring of blood glucose yields considerably more information than intermittent sampling during open-heart surgery; rapid changes in glucose homeostasis occur, and continuous monitoring is ideally suited for the study of glucose metabolism in this situation. The technique may prove to be a valuable tool in the further assessment of per- and postoperative glucose dynamics in such patients, as, for example, when different pump priming fluids are used, or when different perfusion techniques are utilized.

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FACTORS AFFECTING TRAIN-OF-FOUR FADE

A. C. PEARCE, W. R. CASSON AND R. M. JONES

SUMMARY

The characteristics of the train-of-four response during neuromuscular blockade with two agents, atracurium and vecuronium, have been compared. During onset of blockade, at 75% depression of the initial twitch, atracurium was associated with significantly more fade than was vecuronium, and larger doses of atracurium were associated with less fade than smaller doses of the same agent. In addition, with both agents, the degree of fade at a given amount of initial twitch depression was significantly less during onset than during spontaneous offset of action. The degree of train-of-four fade bears no fixed relationship to depression of the initial twitch.

The use of a train-of-four (TOF) pattern of stimultion (Ali, Utting and Gray, 1970) to detect and quantify neuromuscular blockade has become firmly established. It has been suggested that a relationship exists between the degree of single, or initial, twitch depression and the amount of TOF fade or number of responses within the train (Lee, 1975). However, more recently, the variability of this relationship with the same neuromuscular blocker during onset and spontaneous offset of neuromuscular blockade has been demonstrated (Bowman, 1980). In addition, Williams, Webb and Calvey (1980) have demonstrated that individual neuromuscular blocking drugs may be associated with varying degrees of train-of-four fade during the onset of neuromuscular blockade; these authors have speculated that this observation may be attributable to the action of such drugs at more than one site within the neuromuscular junction.

We have compared the pattern of TOF fade of two neuromuscular blocking drugs, atracurium and vecuronium, during both onset and spontaneous offset of neuromuscular blockade, and also studied the fade characteristics of varying doses of atracurium during onset of action.

PATIENTS AND METHODS

After ethics committee approval and with informed consent, we studied patients undergoing surgery requiring the use of neuromuscular blocking drugs. No patient of greater than 20% above ideal weight was included in the study. Neuromuscular monitoring was undertaken in a standard manner using the same recording equipment for all patients.

Before induction of anaesthesia, the left arm of the subject was immobilized in a splint and a force displacement transducer (Grass FTO3C) was attached to the thumb. The force of contraction of adductor pollicis following ulnar nerve stimulation was recorded using a Devices pre-amplifier and two-channel chart recorder. The linearity of the recording system in the range 0.05–2.0 kg was confirmed by the use of weights. Stimulation of the ulnar nerve was by supramaximal 0.2-ms square wave impulses delivered in a train-of-four pattern at 2 Hz for 2 s via surface electrodes at the wrist, repeated at 12-s intervals (Myotest).

Two indices of neuromuscular blockade were recorded: the height of the first, or initial, response in the train (T1) compared with control T1 (T1:control) (%) and the ratio of the height of the fourth to the height of the first response in the same train (T4 ratio). Because of the 10-s interval between trains, the first response was considered to be an unmodified single twitch response.

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The basic anaesthetic technique in all patients was as follows. Patients were unpremedicated. Anaesthesia was induced with 2.5% thiopentone injected via an indwelling needle on the dorsum of the right hand, in a dose approximately 20% greater than that required to abolish the eyelash reflex. After baseline neuromuscular recordings had been made, the neuromuscular blocking drug was injected via the same needle, preceded and flushed with saline 1 ml (time 0). The patients received nitrous oxide in oxygen (2:1) with 3% enflurane through a face mask and Bain type co-axial breathing system until intubation of the trachea at 3 min, at which time the inspired concentration of enflurane was reduced to 1% and continued at this value until completion of the recording.

In the first part of the study, either atracurium 0.25 mg kg^{-1} or vecuronium 0.06 mg kg^{-1} was randomly administered ($n = 10$ in each group). (Published data suggest that these doses of the two neuromuscular blocking drugs are approximately equipotent.) The T4 ratio of trains with T1:control values nearest to 75%, 50% and 25% were recorded during onset and spontaneous offset of neuromuscular blockade.

In the second part of the study, atracurium 0.25 mg kg^{-1}, 0.375 mg kg^{-1} or 0.5 mg kg^{-1}, was randomly allocated ($n = 10$ each group). The T4 ratio of trains with T1:control values of 25% and the time to achieve this T1:control value were recorded.

Statistical analysis was with Student's t test, paired or unpaired as applicable.

RESULTS

All results are expressed as mean (SD). The ages and weights of the groups in the first part of the study were not significantly different: atracurium, (A) 31.2(9.4) yr, 63.8(9.9) kg; vecuronium (V) 22.8 (10.1) yr, 62.1(10.1) kg ($n = 10$ each group).

The T4 ratios at T1:control values of 75%, 50% and 25% during onset and offset of blockade are compared in table I. During onset, the degree of fade at T1: control 25% was greater with atracurium than with vecuronium ($P < 0.05$). With both neuromuscular blockers, there was significantly more fade during offset than during onset at all three chosen values of T1:control ($P < 0.001$ all sets) (table II).

Variations in T4 ratio at T1:control 25% with different doses of atracurium are shown in table III. With atracurium 0.25 mg kg^{-1}, the mean (SD) T4 ratio was 0.26(0.06); with atracurium 0.375 mg kg^{-1} it was 0.53(0.11); and with atracurium 0.5 mg kg^{-1}, 0.65(0.06). Thus the largest dose of atracurium was associated with significantly less fade than was either the middle ($P < 0.01$) or the smallest dose ($P < 0.001$).

TABLE I. *Comparison between atracurium 0.25 mg* kg^{-1} *and vecuronium 0.06 mg* kg^{-1}*, during both onset and offset of neuromuscular blockade. Mean (SD) T4 ratio at T1:control 75%, 50% and 25%.*
**Degree of fade with atracurium significantly greater than with vecuronium* ($P<0.05$)

	Onset		Offset	
T1:control	A	V	A	V
75%	0.71 (0.08)	0.74 (0.06)	0.36 (0.14)	0.31 (0.09)
50%	0.50 (0.15)	0.62 (0.13)	0.19 (0.15)	0.16 (0.09)
25%	0.26 (0.17) *	0.44 (0.18)	0.06 (0.11)	0.02 (0.02)

TABLE II. *The same data as in table I, arranged to show a comparison between onset and offset, for both atracurium 0.25 mg* kg^{-1} *and vecuronium 0.06 mg* kg^{-1}*. The difference between mean (SD) T4 ratios during onset and offset at each T1:control value for both drugs is significant* ($P<0.001$)

	Atracurium		Vecuronium	
T1:control	Onset	Offset	Onset	Offset
75%	0.71 (0.08)	0.36 (0.14)	0.74 (0.06)	0.31 (0.09)
50%	0.50 (0.15)	0.19 (0.15)	0.62 (0.13)	0.16 (0.09)
25%	0.26 (0.17)	0.06 (0.11)	0.44 (0.18)	0.02 (0.02)

TABLE III. *Individual and mean (SD) T4 ratio at T1:control 25% with different doses of atracurium, during onset of blockade*

	Dose of atracurium		
	0.50 mg kg^{-1}	0.375 mg kg^{-1}	0.25 mg kg^{-1}
	0.53	0.68	0.21
	0.60	0.60	0.26
	0.63	0.56	0.00
	0.73	0.50	0.25
	0.75	0.45	0.23
	0.67	0.46	0.28
	0.66	0.44	0.68
	0.65	0.52	0.25
	0.60	0.36	0.23
	0.63	0.70	0.23
Mean (SD)	0.65 (0.06)	0.53 (0.11)	0.26 (0.06)

DISCUSSION

The train-of-four mode of stimulation is commonly used in research and clinical practice to determine the degree of neuromuscular blockade. It is more sensitive than the single twitch response and as sensitive as a 50-Hz tetanus (Ali, Lebowitz and Ramsey, 1981). Observation of the number of responses within a train, or calculation of a train-of-four ratio will delineate the degree of blockade without reference to a control train-of-four response; the absolute force of contraction of the responses in a train, however, can only be compared with the patient's normal response if a control train-of-four has been obtained. Working with tubocurarine, Lee (1975) showed that the response to the fourth stimulus disappeared when the first response had been reduced to 20–25% of control, during onset of blockade. This correlation between initial, or single twitch, depression and train-of-four fade is often cited without reference to the drug and its concentration, or the phase of blockade (Miller and Savarese, 1981; Viby-Mogensen, 1982).

The results of the present study demonstrate that the train-of-four ratio and the depression of the single twitch bear no fixed relationship. The relationship varied between neuromuscular blocking agents and during onset and offset of blockade. Atracurium caused more fade than vecuronium during onset, and both drugs exhibited more fade during offset than during onset. Our results confirm the greater degree of fade during offset previously described with vecuronium (Bowman, 1980).

Single twitch depression and train-of-four fade may be the results of neuromuscular blockers binding to different sites. Bowman (1980) suggested that fade may be an expression of prejunctional receptor binding, impairing transmitter mobilization during rapid stimulation. Another possibility is that the neuromuscular blocking drug plugs open sodium channels at, or near, prejunctional receptors. This will occur in a use-dependent fashion, being therefore more marked at high rates of stimulation (Standaert, 1982). The single twitch response appears to be more a function of postsynaptic binding. Certainly, the prejunctional receptors appear to be structurally disparate from the postjunctional receptors, and have more similarity with ganglionic cholinoceptors. It is not surprising that different neuromuscular blocking drugs will have differing affinities for pre- and postjunctional binding sites and will therefore affect the train-of-four response in different, but characteristic, patterns. Atracurium causes more fade than vecuronium during onset at T1:control 25% and therefore has greater activity at fade "receptors", wherever these may be within the neuromuscular junction. No significant difference between the two agents was demonstrated at T1:control 75% and 50%; this may have been because the size of the study groups was too small to reveal a statistical significance of the small differences at these stages.

The rate of binding to the single twitch and fade "receptors" was different also. With both neuromuscular blockers there was more fade at each value of T1:control during offset than during onset, suggesting that the rate of binding or expression of binding occurs more slowly at fade "receptors". The

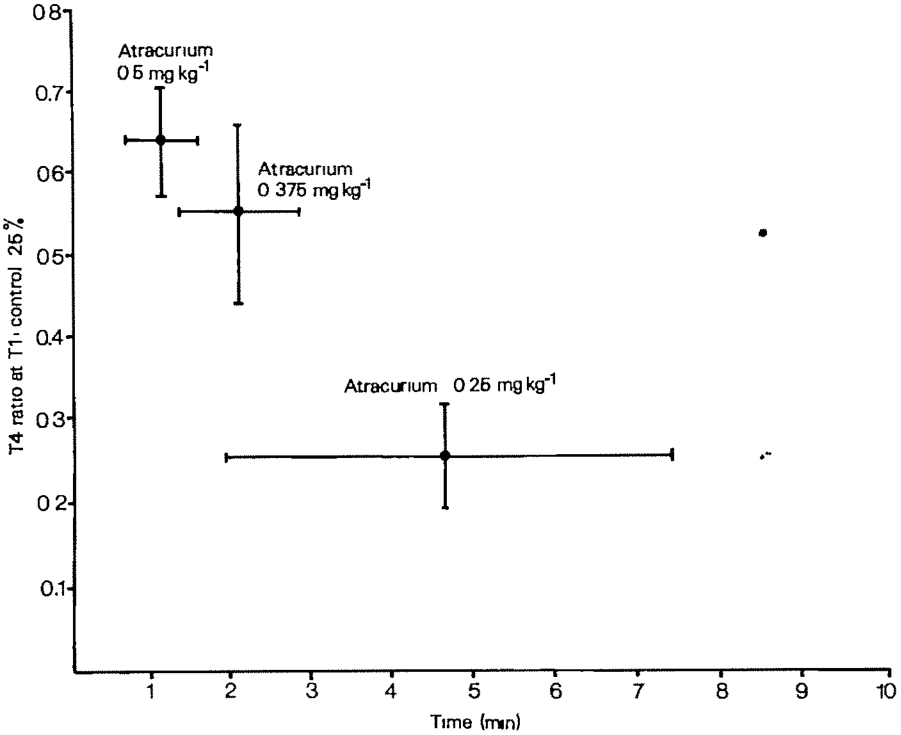

FIG 1. Association between T4 ratio and T1:control 25% and the time taken to achieve this T1:control value (mean (SD)).

pharmacodynamics of neuromuscular blocking drugs at the neuromuscular junction are complex (Hull, 1982). Drug must diffuse through the biophase to reach the receptor. The rate of diffusion will be affected by blood concentration, and the disparity between activity at single twitch and fade "receptors" may be enhanced by varying the dose of drug. In this study, larger doses of atracurium were associated with less fade at T1:control 25% than were smaller doses, during onset of blockade. However, alterations in dose vary the time taken to achieve a certain degree of blockade, and it is not possible from this study to separate the effects of dose and of time on fade. Figure 1 shows, for the three doses of atracurium, the mean values of the association between the T4 ratio at T1:control 25% and the time to achieve this T1:control value, and also demonstrates the greater variability of onset times as the dose was reduced.

It should be noted that enflurane is known to potentiate the action of neuromuscular blocking agents and may itself have effects within the neuromuscular junction (Waud and Waud, 1975). However, it is unlikely that this volatile agent could have exerted significant effects during the few minutes of onset of blockade in the present study. In addition, all patients were exposed to the same inspired concentration of enflurane throughout the study period, and Bowman (1980) has previously demonstrated a similar difference between onset and offset with vecuronium in the absence of enflurane.

The finding that the relationship between depression of the initial twitch and fade is not fixed is of importance. In clinical practice the magnitude of the train-of-four ratio is often used at the end of surgery to assess the degree of residual blockade and the requirement for pharmacological antagonism. A safe value is generally accepted to be of the order 0.5–0.75. However, it is really the absolute height (force of contraction) of the fourth and therefore subsequent twitch response which is important in determining sustained muscle power. With different neuromuscular blocking drugs, at an identical T4 ratio, the magnitudes of the first, and therefore the fourth, twitch responses will be different. This raises the possibility that different agents possess an individual "safe" T4 ratio which incorporates the fade characteristics of the agent, but since the T4 ratio may not accurately quantify the degree of blockade, comparisons between studies using this mode of stimulation may give rise to erroneous conclusions. Perhaps the fourth twitch:control fourth twitch (T4:control) value would have more clinical relevance.

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RAPID INDUCTION OF HALOTHANE ANAESTHESIA IN MAN

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The inhalation induction of general anaesthesia is usually avoided by both patients and anaesthetists, since a prolonged induction may terrify both adults and children. In addition, the anaesthetist may have difficulty maintaining the airway and restraining the muscular patient if excitement occurs. Intravenous induction is popular because these complications are usually avoided. However, venous access may be impossible in some patients and the slow termination of action of i.v. agents may delay the awakening of patients following outpatient surgery. In the past, cyclopropane offered an alternative (Bourne, 1954): loss of consciousness was rapid, arterial pressure was well maintained and emergence was rapid. The risk of explosion has, however, forced most anaesthetists to discard this method of rapid induction.

To provide a better method of gaseous induction of anaesthesia in co-operative adults, we devised a new halothane in oxygen technique. The patient takes a vital capacity breath of 4% halothane in oxygen and attempts to hold his breath until he is unconscious. The method has been used in approximately 200 patients in the past 5 years and appears to be effective, safe and acceptable. To understand this technique better, we attempted to anaesthetize healthy volunteers using vital capacity breath-holds of various concentrations of halothane in oxygen as delivered by clinical equipment, while monitoring cardiopulmonary responses.

SUMMARY

The cardiopulmonary and anaesthetic responses of nine healthy volunteers, breathing concentrations of 1–4% halothane in oxygen, were studied. Supine fasting subjects breathing room air exhaled to residual volume and then inhaled a vital capacity breath of 1, 2, 3 or 4% halothane in oxygen. After a breath-hold of 30–90 s they exhaled and then breathed spontaneously the same anaesthetic mixture for up to 2 min. The electrocardiogram, arterial pressure, heart sounds and arterial oxygen saturation, were monitored, and respiratory gases were analysed by mass spectrometry. The maximum effect was seen after breathing 4% halothane. All volunteers were amnesic after the first breath and unresponsive to command after 2 min. Little or no excitement occurred. A maximum decrease of 12 mm Hg in systolic pressure was seen while breathing 4% halothane. Bradycardia, hypoxia and clinically important hypercarbia did not occur. At all inspired concentrations of halothane, the end-tidal halothane concentration increased rapidly and was 30% of the inspired value after 1 min. No volunteer found this technique to be unpleasant. Rapid induction of general anaesthesia with 2–4% halothane in oxygen is effective, safe and well accepted by healthy young adults.

SUBJECTS, MATERIALS AND METHODS

Selection of volunteers

Following approval by our Human Studies Committee, nine healthy men and women, aged 20–45 yr, were recruited. No volunteer had a history of liver disease and each had normal haematological values, serum bilirubin concentration, alkaline phosphatase concentration, transaminase concent-

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rations, and negative titres for HB_sAg and HB_eAg. Informed consent included specific reference to the possibility of liver disease following exposure to halothane.

Measurements

Heart rate and rhythm were monitored on a standard operating room electrocardiograph. Arterial pressure was measured using an automatic non-invasive monitor (Dinamap No. 845XT with a model No. 950 recorder (Critikon)) (Looney, 1978). Arterial oxygen saturation was estimated using an ear oximeter (Biox model No. 11 A) (Fahey et al., 1983). Oxygen, nitrogen, carbon dioxide and halothane were detected continuously in the inspired and expired gas using a Perkin Elmer mass spectrometer (model MGA 1100A) which was calibrated using gravimetric standards of nitrogen, oxygen, carbon dioxide and halothane contained in compressed gas cylinders (Calibrated Standards, Airco Inc.) The signals were recorded on magnetic discs and processed subsequently on a DEC MINC 11/23 laboratory computer. The inspired concentrations of halothane, and the end-tidal concentrations of halothane (ET_{hal}), oxygen (ET_{O_2}), and carbon dioxide (ET_{CO_2}) were tabulated on a breath-by-breath basis. Arterial oxygen saturation (Sa_{O_2}), heart rate (HR) and arterial pressure were noted before induction, after 2 min of breathing halothane, and after awakening.

Anaesthetic apparatus

Mixtures of halothane in oxygen were delivered from a Drager Narkomed 2 anaesthetic machine fitted with either a Drager Halothane 19 or a Vapor vaporizer and a circle system. In place of the Y-connector in the circle, a Collins spirometer valve was used to allow the inspired gas to be switched rapidly between room air and the anaesthetic gas in the circle. The connector between the spirometer valve and the mask was the site for sampling inspired and expired gas for analysis. For each trial the circle was primed for about 2 min at a 10-litre min^{-1} oxygen flow with the vaporizer set at the desired halothane concentration.

Experimental programme

Each volunteer breathed a sequence of four concentrations of halothane in oxygen. Each exposure to halothane lasted no more than 4 min and a recovery period of at least 15 min was allowed between exposures.

After an 8-h fast, the volunteer lay supine on a stretcher and monitoring was commenced. At each anaesthetic concentration the volunteer inhaled a vital capacity breath of air through the mask and then exhaled to residual volume. The Collins valve was opened to the anaesthetic mixture and then, over a 10-s period, the volunteer inhaled (through his mouth) a vital capacity breath of halothane in oxygen from the primed anaesthesia circuit. The breath was taken slowly to avoid collapsing the reservoir bag. After the initial breath, the fresh gas flow was reduced to 5 litre min^{-1} to minimize positive pressure in the circle. After a breath-hold of 30–90 s the volunteer exhaled and then breathed spontaneously. He indicated the onset of tinnitus by a hand signal. After the breath-hold the same halothane in oxygen mixture was inspired for a maximum of 2 min. The Collins valve was then opened to room air and the volunteer emerged from anaesthesia.

Each volunteer inspired five mixtures of halothane and oxygen. Between trials the subject recovered until his expired halothane concentration was less than 0.01% and he felt fully awake. Four percent halothane in oxygen was administered first to determine a comfortable breath-hold time for subsequent trials, to accustom the volunteer to the experience of general anaesthesia, and to ascertain if the maximum inhaled concentration could be tolerated. The four subsequent trials of 1, 2, 3 and 4% halothane in oxygen were given in a random order to avoid biasing responses by a cumulative effect of halothane. In addition, the subjects were blind to the concentration of halothane. Onset of unconsciousness was defined as the time at which the subject would no longer open his eyes to verbal command. This command was repeated every 15 s until the subject no longer responded. Onset of awakening was defined as the time at which the subject first opened his eyes to verbal commands repeated at 15-s intervals.

Data analysis

The end-tidal halothane concentrations (ET_{hal} were evaluated by analysis of variance (ANOVA) to ascertain the effect of individual differences in volunteers S_i; nominal inspired halothane concentration, C_j; order of treatments administered, O_k; carry over effect from the halothane concentration of preceding trials, R_l; and finally breath number, X_{ijklm} (Winer, 1971). The model for the average response over all breaths $(ET_{hal})_{ijklm}$ was similar to that for a change-over design balanced for residual effects (John, 1971) with $(\mathrm{ET}_{\mathrm{hal}})_{ykhm} = S_i + C_j + O_k + R_l + e_{ykl} + \beta_j X_{ykhm} + \beta_k X_{ykhm} + f_{ykhm}$

The e_{ykl} error term represented the error variation among the trials and formed the error term for testing the above factors. The order factor was used to test for a cumulative effect over the five trials. The carry-over effect tested whether the concentration during the previous trial left a residual effect on the current trial. β represents the overall linear slope and β_j the separate slopes for the different halothane concentrations. The term f_{ykhm} represents the repeated measures error across all trials. The terms in the model indexed by *m* represent the repeated measures made after breaths 1–5 and at 2 min. Three conditions were defined for analysis of cardiopulmonary responses. These included before induction, during anaesthesia and after awakening. ANOVA was used to evaluate the effects of subject, inspired halothane concentrations, condition and all first order interactions.

Because three observations were lost as a result of instrumentation malfunctions, calculations were adjusted for unbalanced and missing data using the general linear model routine in the SAS statistical package (Helwig and Council, 1979). All trials for subjects were considered stochastically independent. Diagnostic plots verified the assumption of homoscedastic errors. For all tests a value of $P < 0.01$ was considered statistically significant.

RESULTS

During the induction of anaesthesia the inspired halothane concentrations, measured at the connector to the mask, were always greater than the vaporizer settings (table I). The relative percentage errors varied inversely with concentration and ranged from ±19.0 to ±6.1%.

End-tidal halothane concentrations increased rapidly and linearly with successive breaths at all inspired concentrations of halothane greater than 1% (fig. 1). However, at 1% halothane, the end-tidal concentrations appeared to plateau after the second breath. The slope of the 1% data was zero while the slopes of the 2%, 3%, and 4% data were greater than zero and did not differ significantly from each other ($P < 0.01$, F test). With subjects breathing 4% halothane, the mean end-tidal concentration was 1.5% at the end of the fifth breath. We observed a significant difference in the time course of end-tidal halothane between subjects (table II). There was no carry-over between successive trials of halothane exposure.

There were differences among subjects before induction in arterial pressure, heart rate, $\mathrm{ET}_{\mathrm{O_2}}$, $\mathrm{ET}_{\mathrm{CO_2}}$, and arterial oxygen saturation, but these differences failed to influence the cardiopulmonary responses to halothane. Maximum changes in all variables were seen with 4% halothane (table III). Although decreases in arterial pressure were statisti-

TABLE I. *Vaporizer output of halothane. Pooled values (mean±SD) from Drager Halothane Vapor 19 and Vapor vaporizers at room temperature* *P<*0.01 when delivered value was compared with nominal setting (unpaired* t *test)*

Nominal setting (%)	Delivered value (%)	Number of observations
1.0	1.42±0.27*	8
2.0	2.33±0.20*	9
3.0	3.28±0.23*	9
4.0	4.26±0.26*	15

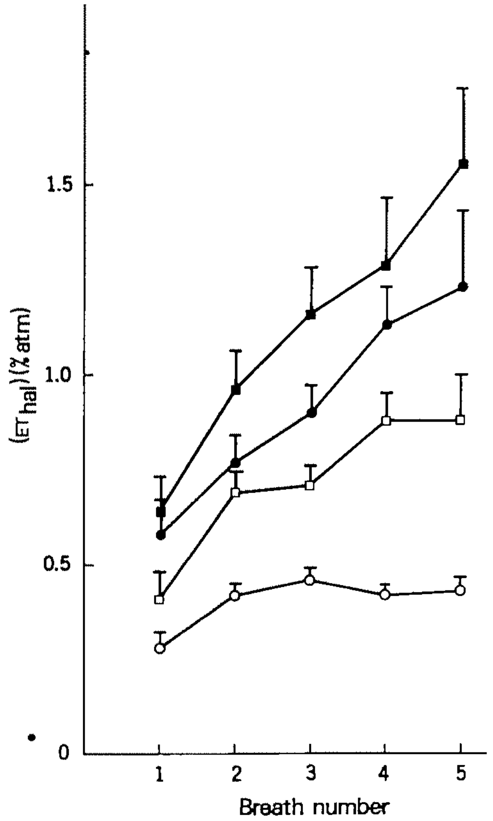

FIG 1. The end-tidal concentration of halothane ($\mathrm{ET}_{\mathrm{hal}}$) (mean values ± SEM) increased linearly with each successive breath at inspired concentrations of 2% (□), 3% (●) 4% (■). At 1% (○) inspired concentration a plateau was reached by the third breath.

TABLE II. *ANOVA for end-tidal halothane. (df = degrees of freedom for* f *test,* F = *caculated variance ratio)*

Source of variance	df	Mean square	*F*	*P*
Subject	8	0.236	2.57	0.040
Concentration	3	0.380	4.14	0.019
Order	4	0.169	1.84	0.159
Carry over effect	3	0.064	0.70	0.564
Error	21	0.0918	—	—
Breath number	1	7.561	161.9	0.0001
Concentration × breath number	3	0.456	9.69	0.0001
Repeated measures error	159	0.0467	—	—

cally significant, their magnitude was small. The greatest change was in systolic pressure and was less than 12 mm Hg. Heart rate did not change and no arrhythmias were observed. Inspired and expired oxygen tensions increased during induction and returned toward normal with awakening. Oxygen saturation remained stable during induction but decreased slightly while volunteers breathed room air during emergence. The vital capacity manoeuvre with room air decreased end-tidal carbon dioxide concentration to 4.5 kPa before induction. The end-tidal carbon dioxide concentration at the end of breath holding was 6.2 kPa.

The number of patients failing to respond to verbal command increased with breath number and percent inspired halothane (table IV). The onset of unconsciousness was rapid and was achieved in 15 of 16 trials after breath-hold plus 2 min of breathing 4% halothane. This represented 3.5 min of anaesthesia time. Although in only two of 16 trials were the volunteers unconscious at the end of the breath-hold of 4% halothane, they were unconscious in 10 of 16 trials by the fifth breath of 4% halothane. While breathing 2% halothane, seven of nine subjects were unconscious by 2 min.

TABLE III. *Cardiopulmonary responses of nine volunteers to a vital capacity breath of 4% inspired halothane followed by 2 min of spontaneously breathing 4% halothane (mean±SEM). Arterial pressures were measured at the end of the 2-min period. Saturation and gas concentrations were measured at the end of the breath hold.* *P<*0.02 compared with before induction (paired* t *test)*

	Before induction	During anaesthesia	After awakening
Mean pressure (mm Hg)	86±3	79±3*	87±5
Systolic pressure (mm Hg)	125±3	113±2*	123±4
Diastolic pressure (mm Hg)	73±3	67±4*	67±4
I_{O_2} (atm)	0.21±0.00	0.95±0.01*	0.21±0.00
ET_{O_2} (atm)	0.18±0.01	0.58±0.05*	0.24±0.01*
S_{O_2} (%)	97.3±0.5	99.2±0.4	94.8±0.8*
ET_{CO_2} (kPa)	4.5±0.4	6.2±0.3	5.5±0.2

TABLE IV. *Number of breaths or time required to produce unconsciousness at different inspired concentrations of halothane*

Inspired halothane (%)	Number unconscious/Number of trials			
	First breath	Fifth breath	1 min	2 min
1	0/8	1/8	0/8	1/8
2	0/9	2/9	2/9	7/9
3	1/9	3/9	5/9	8/9
4	2/16	10/16	12/16	15/16

DISCUSSION

Gaseous induction by a single vital capacity breath of 4% halothane in oxygen followed by 2 min of breathing the same mixture produced unconsciousness rapidly in healthy young volunteers without clinically important hypotension, arrhythmia, hypercarbia or hypoxia. Our volunteers found the experience relatively pleasant and stated they would accept this method for clinical anaesthesia. Indeed, those previously anaesthetized with either an i.v. induction or a conventional gaseous induction with gradually increasing concentrations of anaesthetic, expressed a clear preference for the single-breath technique.

This approach to anaesthesia is reminiscent of the gaseous induction of anaesthesia with cyclopropane: because of its low solubility and relatively high potency, both induction and awakening were rapid (Bourne, 1954). Our data demonstrate that this method of induction using halothane is similarly rapid and suggests that, in addition, in an unpremedicated patient awakening is rapid after a short anaesthetic. Variations in time to unconsciousness and rate of increase in end-tidal halothane concentrations among volunteers have several explanations. The minimum alveolar concentration (MAC) decreases with age (Stoelting, Longnecker and Eger, 1970). Since our volunteers ranged in age from 20 to 45 yr, we might expect the youngest volunteers to be least readily anaesthetized. This was not the case. Variable anaesthetic uptake may result if residual volume or vital capacity are not reached during induction. Specifically, if the initial breath is less than vital capacity, a submaximal amount of halothane is available for uptake. If the first exhalation fails to reach residual volume, the subsequent breath of halothane and oxygen to the vital capacity point must be diluted with more air. Hence the subject's alveolar halothane concentration, at peak inspiration, is lower and there is less anaesthetic effect. Finally, variations in inspired halothane concentration supplied by vaporizers may occur. We were surprised at the discrepancy between the nominal vaporizer settings and actual concentration of halothane delivered as measured by the mass spectrometer (table I). Some of the variation seen between subjects may be related to differences between nominal and actual inspired anaesthetic concentrations.

Although it was difficult to measure precisely, the onset of amnesia occurred substantially earlier than the onset of unconsciousness. Volunteers usually remembered only the first breath, even when obeying commands after the fifth breath of halothane. We believe that this early onset of amnesia may be an important factor in acceptance and also contributes to the flexibility of this technique. A concentration of halothane as low as 2% is often adequate. This is a potential advantage because 2% halothane is less irritating to breathe than 4%. However, several of the volunteers preferred the induction using 4% halothane because it was more rapid. Only one volunteer found the halothane sufficiently irritating to cause coughing, but the coughing did not delay induction.

Our data are consistent with previous descriptions of halothane uptake and minimum alveolar concentrations (Gregory, Eger and Munson, 1969; Nicodemus et al., 1969; Stoelting, Longnecker and Eger, 1970). There appears to be enough uptake after five breaths or 2 min following a 30–90 s breath-hold to achieve adequate anaesthetic concentrations in the brain. The increase in expired carbon dioxide at the end of a vital capacity breath-hold of 4% halothane was 1.7 ± 0.3 kPa. Eger and Severinghaus (1961) measured an increase of 1.8 ± 0.3 kPa after the first 1 min of apnoea in anaesthetized patients.

These investigations were carried out on healthy volunteers, and our clinical experience with this technique has been with patients of ASA status I and II. This method of induction offers real benefits to patients having brief procedures, in achieving both rapid onset of unconsciousness and fairly prompt awakening. Patients in whom venous access is difficult can be anaesthetized painlessly and safely before the i.v. access is established. At present, we regard patients with poor lung function having large ventilation/perfusion mixmatches, greatly reduced vital capacity or excessively large functional residual capacity as poor candidates for this particular technique. In addition, the young, the retarded, the senile and others who cannot or will not perform the necessary steps are unsuitable, because co-operation is required. Premedication with, for example, benzodiazepines, or barbiturates and narcotics is compatible, but may modify the breath-hold time and delay the resumption of regular breathing because of the respiratory depressant effects of these drugs (Patrick and Faulconer, 1952; Smith et al., 1967; Gross, Smith and Smith, 1982).

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DIFFERENTIAL NERVE BLOCKING ACTIVITY OF AMINO-ESTER LOCAL ANAESTHETICS

J. A. W. WILDSMITH, A. J. GISSEN, J. GREGUS AND B. G. COVINO

SUMMARY

The in vitro *sensitivities to local anaesthetic blockade of A, B and C nerve fibres in rabbit vagus nerves were examined using a series of structurally similar amino-ester agents which varied in lipid solubility and anaesthetic potency. A fibres were found to be the most sensitive and C fibres the least sensitive to conduction blockade with all the agents, provided that equilibrium blockade was allowed to develop. A correlation existed between the intrinsic anaesthetic potency of the various agents and their lipid solubilities. Equipotent concentrations of the drugs blocked C fibres at approximately the same rate, but there were marked variations in the rate at which A fibres were blocked. Amethocaine, an agent of high lipid solubility, blocked A fibres more quickly than C. As lipid solubility decreased through the series studied, so the onset of conduction blockade of A fibres was prolonged. It is suggested that this related to decreasing ability to penetrate the lipid diffusion barriers around A fibres. The traditional view that C fibres were more sensitive to block may have arisen because of confusion between absolute sensitivity and rate of development of conduction blockade.*

The fibres found in peripheral nerves are classified as types A, B or C according to their sizes and conduction velocities (Ganong, 1983). The most rapidly conducting (A) fibres are the largest in diameter and have thick myelin sheaths, whereas the slowest conducting (C) fibres are the smallest, and are unmyelinated. B fibres are lightly myelinated and intermediate in conduction velocity. Traditionally, it has been believed (deJong, 1980) that C fibres are more sensitive to the action of local anaesthetics than A fibres, even though the latter are more susceptible to other factors which block reversibly, such as cold and pressure. Clinical observations have shown that, in general, the vegetative modalities of sensation (usually considered to be transmitted by C fibres) are blocked more easily than the more discriminatory modalities or motor function (both transmitted by A fibres). This has supported the older views on axon sensitivity.

Recent laboratory studies, using an *in vitro* rabbit vagus nerve preparation, found that the sensitivity of these fibre types to blockade by local anaesthetic agents was related directly to their speeds of conduction. A fibres were the most sensitive and C fibres the least (Gissen, Covino and Gregus, 1980; Fink and Cairns, 1983). These studies were concerned primarily with amide type local anaesthetics, whereas most of the early clinical observations on which the traditional views were based were made with the amino-ester agent, procaine (Heinbecker, Bishop and O'Leary, 1934; Sarnoff and Arrowood, 1946). Therefore, the present study was instituted to examine the *in vitro* differential blocking activity of a series of amino-ester agents.

MATERIALS AND METHODS

Albino rabbits of approximately 2 kg weight were sacrificed by air embolism immediately following the administration of sodium thiamylal 25 mg i.v. The cervical vagus nerves were removed within 15 min and subsequently kept immersed in HEPES-Liley solution (table I). The nerves were cleaned and desheathed by microdissection before mounting in an airtight chamber (fig. 1). Petroleum

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jelly seals separated a 1-cm length of the nerve from platinum wire stimulating and recording electrodes. The central section of the chamber (volume 0.25 ml) was perfused with HEPES-Liley solution at 0.5 ml min^{-1} and the other sections were moistened, but not filled, with the same solution.

TABLE I. *Constituents of the perfusing solutions. *HEPES = [4-(2 hydroxyethyl)-1-piperazine–ethane sulphonic acid] pK 7.55 at 20 °C (7.31 at 37 °C)*

	HEPES-Liley	Carbonated-Liley
NaCl (mmol $litre^{-1}$)	136.8	136.8
KCl (mmol $litre^{-1}$)	5.0	5.0
$CaCl_2 \cdot 2H_2O$ (mmol $litre^{-1}$)	2.0	2.0
$MgCl_2 \cdot 6H_2O$ (mmol $litre^{-1}$)	1.0	1.0
Glucose (mmol $litre^{-1}$)	11.0	11.0
$NaHCO_3$ (mmol $litre^{-1}$)	—	15.0
$NaH_2PO_4 \cdot H_2O$ (mmol $litre^{-1}$)	—	1.0
HEPES buffer* (mmol $litre^{-1}$)	3.0	—
Aeration	100% oxygen	95% oxygen 5% carbon dioxide
pH (mean ± range)	7.4±0.02	7.4±0.02
Notes:	pH adjusted by addition of NaOH 0.1 mol $litre^{-1}$ (approx. 15ml $litre^{-1}$)	Aerated 30 min (at least) to reach stable pH values

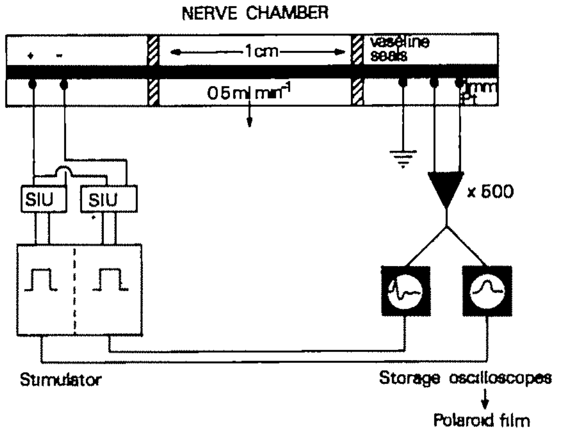
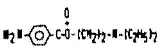
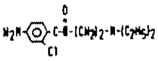
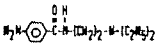
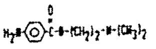
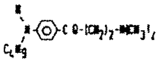


FIG 1. Schematic diagram of the nerve chamber and the equipment used.

A twin-channel square-wave generator (Grass S88) was used to stimulate the nerve via isolation units (Grass S1U 5). A stimulation duration of 0.05 ms was used for A fibres (by definition those in which conduction velocity exceeded 30 m s^{-1}), of 0.1 ms for B fibres (conducting at 5–15 m s^{-1}) and of 1.0 ms for C fibres (conducting at 1 m s^{-1} or less). The stimulus intensities were adjusted (3-6 V for A fibres; 8–15 V for B fibres; 15–25 V for C fibres) to produce maximum action potentials as displayed (fig. 2) on storage oscilloscopes (Tektronix 5113). The signal from the nerve was amplified 500 times (Tektronix AM 502, capacitive coupling) and passed to the oscilloscope pre-amplifiers (Tektronix 5A 21N). The preparation was not considered acceptable unless the compound action potential signals from the nerve exceeded 1.5 mV for A, 1.0 mV for B and 0.3 mV for C fibres.

TABLE II. *Chemical formulae of the drugs used, their pKa values and indices of liquid solubility. pKa values from Buchi and Perlia (1971). a = Distribution coefficient (Buchi and Perlia, 1971); b = partition (Tucker and Mather, 1980).*

Drug		pKa	Lipid solubility a	Lipid solubility b
Procaine		9.02	1.98	0.02
Chloroprocaine		8.96	—	0.14
Procainamide		9.26	0.23	—
Di-MAPA		8.65	0.4	—
Amethocaine		8.48	—	4.1

During a control period of 30 min to ensure stability, one stimulator channel was used to stimulate the A fibres at 0.0167 Hz and to trigger the second channel to stimulate C fibres 10 ms later. At various intervals, the second channel was switched to stimulate B fibres specifically. The same stimulus pattern was used during the subsequent application and wash-out of drug solution. Changes caused by the drugs were monitored on the oscilloscope screens, but all measurements were made from photographs (fig. 2), taken at appropriate intervals, of the traces on the oscilloscope screens.

The effects of various concentrations of the hydrochloride salts of procaine, procainamide (both from ICN Pharmaceuticals, Plainview, NY), chloroprocaine, amethocaine (both from Astra Pharmaceutical Products, Inc., Worcester, MA) and dimethylaminoethylpara-aminobenzoic acid ester (di-MAPA) were studied. Chemical structures and physico–chemical data are shown in table II. The drugs were dissolved in a carbonated-Liley solution (table I) and only one concentration of one drug was applied to individual nerves. Perfusion of test solution through the chamber at 0.5 ml min^{-1} continued for 30 min or until changes in all three compound action potentials achieved equilibrium, whichever was the longer. Once stable blockade was achieved, the nerve was washed with HEPES-Liley solution: recovery of the compound action potentials to 90+% of their control values was required for a valid experiment. All experiments were performed at room temperature.

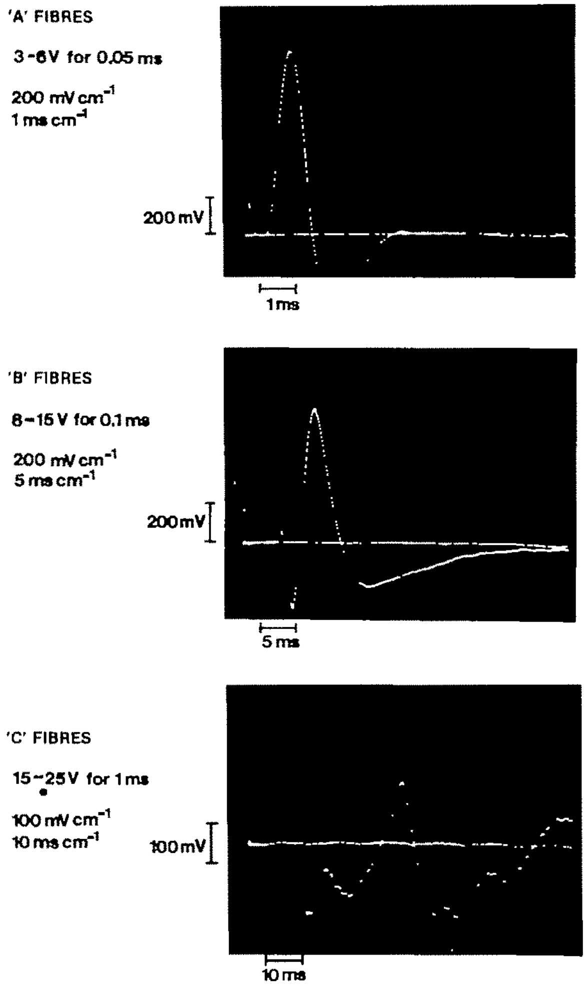


FIG 2. To illustrate compound action potentials of A, B and C fibres from rabbit vagus nerve (amplification × 500).

Changes caused by drugs were measured in terms of the percent decrease produced in the amplitudes of the three compound action potentials from control values. Absolute potency was assessed by the construction of dose–response curves in which the maximal effect on each fibre type was plotted against the concentration of drug on logarithmic–probit graph paper (Miller and Tainter, 1944). The probit scale allows a sigmoid dose–response relationship to be drawn as a straight line and is illustrated in figure 3, with equivalent percent values. Linear regressions of the log of drug concentration against probit score were derived and solved for the point of 50% depression of the action potential amplitude (ED$_{50}$). The standard error (SE) of that value was obtained (Miller and Tainter, 1944). Changes of less than 10% or greater than 90% were excluded from the analysis of these results, since we were interested in the central portion of the dose–response relationship.

Linear plots of the changes in compound action potential amplitude with time (rate of blockade) were made also, photographic records being obtained with particular emphasis on the time taken for 20% decreases to occur. That time was plotted against drug concentration, and regression lines derived, to allow comparison of the rates at which A and C fibre blockade developed. Since the compound action potentials of B fibres were not recorded at less than 5-min intervals, this analysis was not performed.

RESULTS

Figure 3 illustrates the dose–response relationships (derived by least squares regression analysis of the original data) for each drug on A, B and C fibres drawn on log–probit plot. The slopes of the dose–response relationships were steeper for A and B fibres than for C fibres, but there was little variation, with no trends, in the relative effects of individual drugs on the different fibre types.

The ED$_{50}$ of each drug for A, B and C fibres calculated from the dose–response relationships is shown in table III, together with its SE and the number of experiments used in the derivation of these data. With each drug studied, the ED$_{50}$ for A fibres was less than that for B fibres, which was lower than that for C fibres. In every experiment performed the percent decreases in the amplitudes of the compound action potentials were in the order A > B > C, once stable blockade was achieved. There were marked variations in ED$_{50}$ between drugs, their potency increasing from procainamide, through di-MAPA, procaine and chloroprocaine to amethocaine. This pattern was the same with each fibre type.

Figure 4 shows the percent changes in the compound action potentials for A and C fibres in three individual experiments involving approximately equipotent concentrations of amethocaine, procaine

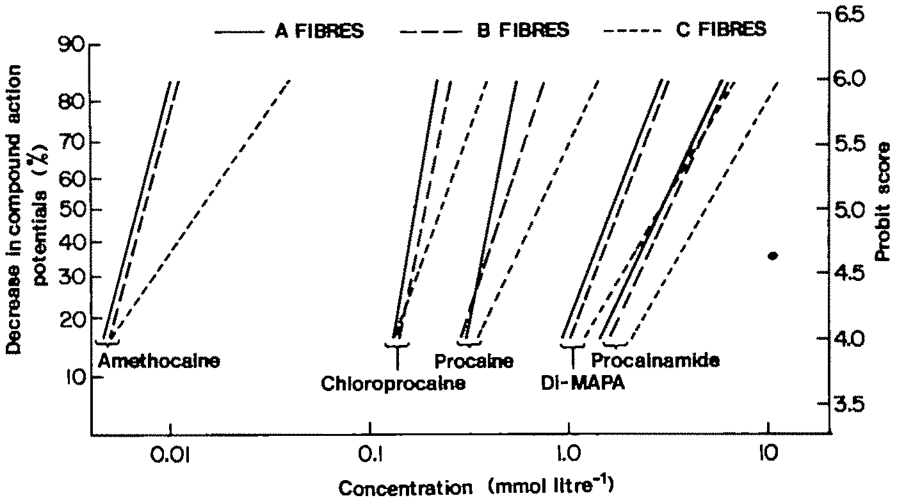


FIG 3. Dose–response relationships for the effect of each drug used on each fibre type. Correlation coefficient for each relationship > 0.87 Desheathed rabbit vagus *in vitro;* carbonated-Liley solution, 23–26 °C, pH 7.4.

TABLE III. *ED_{50} (mmol litre^{-1}) (and its standard error) for the effect of each drug used on each fibre type. n = Number of experiments*

Fibre type	Amethocaine	Chloroprocaine	Procaine	Di-MAPA	Procainamide
A	0.007 (0.002)	0.17 (0.03)	0.41 (0.07)	1.68 (0.41)	2.90 (1.44)
n	5	5	5	5	5
B	0.008 (0.002)	0.20 (0.04)	0.47 (0.12)	1.83 (0.68)	3.22 (1.56)
n	5	6	7	5	5
C	0.014 (0.007)	0.23 (0.007)	0.71 (0.26)	2.87 (1.60)	5.00 (3.0)
n	7	7	8	6	6

and procainamide. The rate of onset of C fibre blockade was of the same order with each drug, but there were obvious differences in the absolute and relative rate of development of A fibre blockade. Amethocaine blocked A fibres faster than C and procaine blocked the two at much the same rate, but with procainamide, A fibre block only started to become apparent after 30 min, and took several hours to stabilize. Figure 5 shows the regression lines of the initial rate of development of A and C fibre blockade (expressed in terms of the time taken for the compound action potentials to decrease by 20%) plotted against concentration for all five drugs. A fibres were blocked faster than C in every experiment with amethocaine, but more slowly than C fibres with di-MAPA and procainamide. There were no consistent differences with either procaine or chloroprocaine.

DISCUSSION

These results confirm earlier work (Gissen, Covino and Gregus, 1980; Fink and Cairns, 1983) that the *in vitro* sensitivity to conduction blockade by local anaesthetics of the fibres found in rabbit vagus nerve is in the order A > B > C. In this study, sensitivity was examined using a series of agents related to procaine and with molecular structures showing specific variations one from another (table II). These structural differences produced variations in absolute potency that were as expected from standard considerations of the structure–activity relationships of local anaesthetics (Buchi and Perlia, 1971). Potency increases when radicals are added to the aromatic ring structure (procaine to chloroprocaine; di-MAPA to amethocaine) or as the length of the alkyl chains attached to the amine group increases (di-MAPA to procaine), or both. Substitution of a nitrogen for an oxygen in the central section of the molecule (procaine to procainamide) reduces potency considerably. These structural changes have possibly their most important physico-chemical effect on lipid solubility which, qualitatively at least, is related to potency. Comparable lipid partition coefficients for all the agents used here are not available, but figure 6 shows data for three of the agents plotted with their ED_{50} for A and C fibres. An excellent correlation exists between the relative lipid solubility of these agents and their conduction blocking potencies.

Although there were marked differences in overall potency, there were only small differences, with no trends, in the relative effect of each drug on the different fibre types. Major differences were found in the *rates* at which the fibre types were blocked by equipotent concentrations of each drug. The time scale of C fibre blockade was of the same order with each agent, but development of A fibre blockade varied considerably. Again, this was related to lipid solubility, with the highly soluble agent, amethocaine, blocking A fibres quickly, whereas the low solubility agents procainamide and di-MAPA blocked them very slowly. It was not possible to follow the development of B fibre blockade in detail, but with the agents of low lipid solubility it was obviously intermediate between A and C.

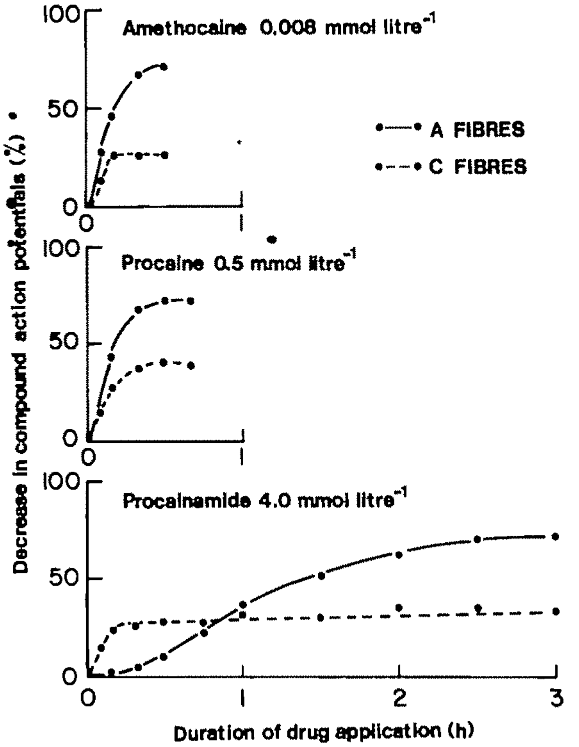


FIG 4. Percent decreases with time in the compound action potentials for A and C fibres of desheathed rabbit vagus *in vitro*, during exposure to specific concentrations of three agents in carbonated-Liley solution, 23–26 °C, pH 7.4

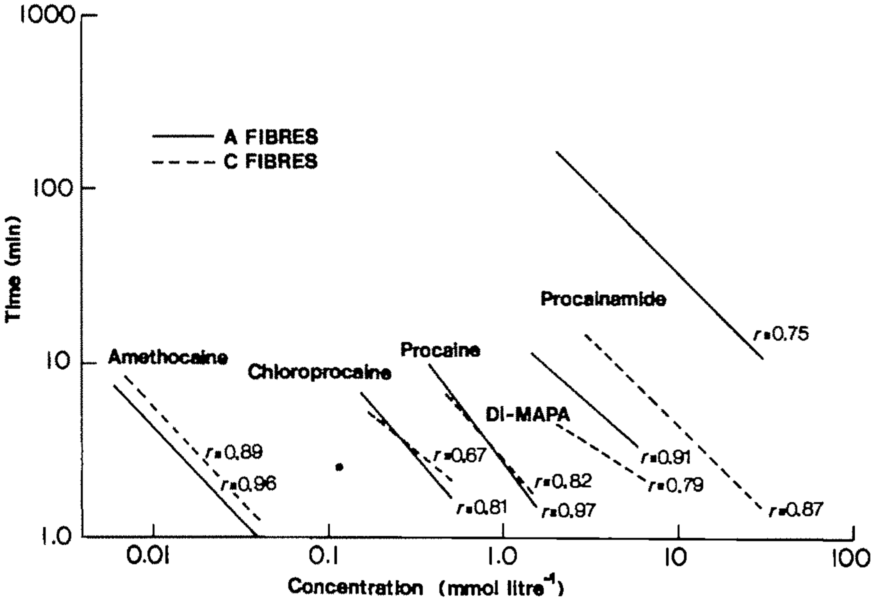


FIG. 5. Relative rate of development of blockade of A and C fibres with five agents expressed as time to develop 20% decrease in amplitude of compound action potentials. Regression lines are drawn only across range of concentrations studied. $n > 5$ for each line.

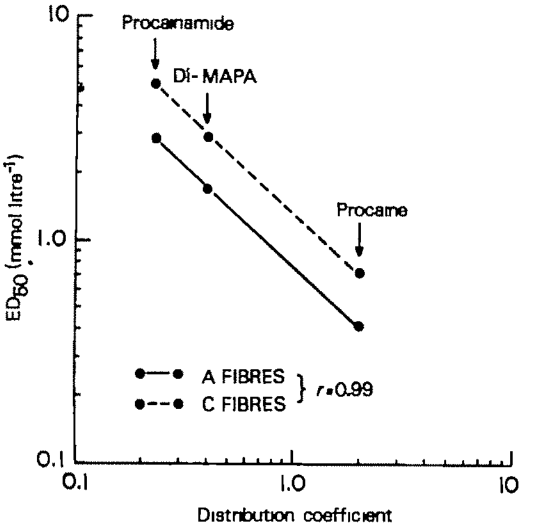


FIG 6. Relationship between ED_{50} and distribution coefficient of three agents.

This slow rate of blocking A fibres with some agents was the reason that the drugs used in the study were applied in a carbonated-Liley solution, rather than dissolved in the HEPES-Liley solution in which the nerves were prepared. Carbon dioxide potentiates the action of local anaesthetics by enhancing diffusion and by decreasing intracellular pH, which increases the intracellular concentration of the ionized, active form of the molecule (Catchlove, 1972). Exposure of the preparation used in this study to the same carbonated-Liley solution without drug had no obvious effect on either the amplitude or speed of conduction of the compound action potential of any fibre type, but the absolute potency of the drugs was increased and the rate of blocking was accelerated.

Figure 7 shows C fibre dose–response curves for amethocaine, procaine and procainamide dissolved in HEPES-Liley obtained in some preliminary experiments, compared with those using carbonated-Liley from figure 3. In each case there was some potentiation, with the effect being more marked with the drugs of lower lipid solubility. Figure 8 compares the rate of development of A and C fibre blockade in some individual experiments with equal concentrations of amethocaine, procaine and procainamide in either HEPES-Liley or carbonated-Liley. Again, the potentiation of rate of development was far more marked with the drugs of low lipid solubility. The very slow rate of onset of A fibre blockade in this preparation when the low lipid solubility drugs were dissolved in HEPES-Liley gave rise to doubts as to the viability of the preparation when used over such long periods of time and, therefore, a carbonated solution was used for all drugs, to enable valid comparisons to be made.

A fibres are surrounded by considerably greater barriers to diffusion than are C fibres. The multilayered lipoprotein membranes of the myelin sheath are present along the greater part of their length, but the original view that there are no such coverings at nodes of Ranvier is incorrect. While recent work has confirmed that the myelin sheaths derived from

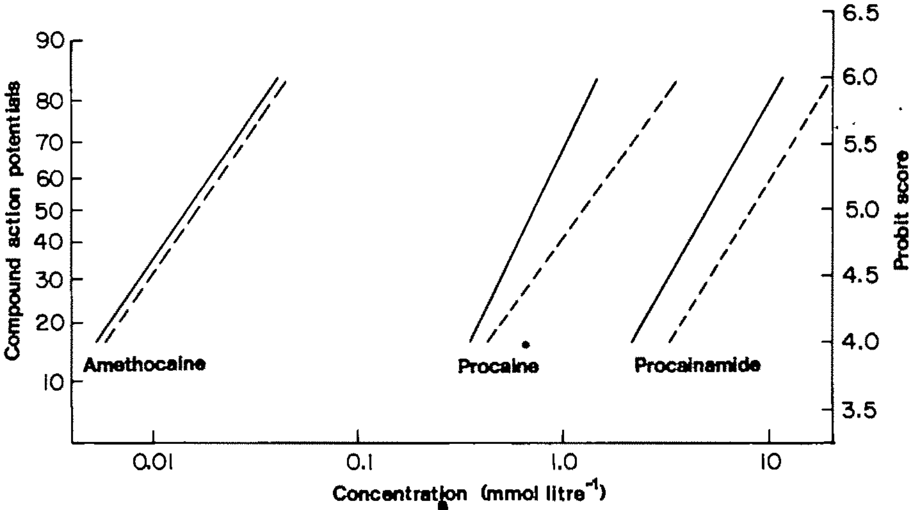


FIG. 7. Dose–response relationships for C fibres of desheathed rabbit vagus nerve exposed *in vitro* to three agents dissolved in either HEPES-Liley (---) or carbonated-Liley (——) solution, 23–26 °C, pH 7.4.

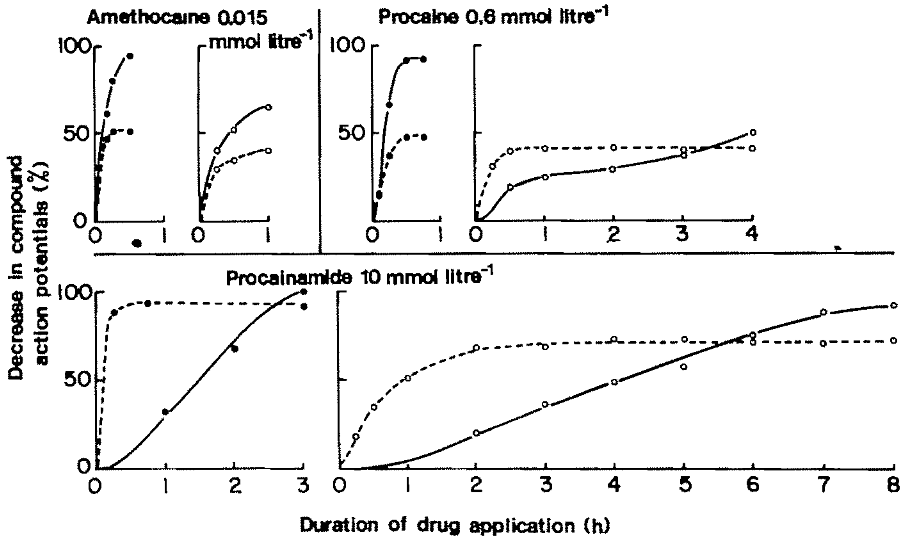


FIG 8. To compare rate of development of A (——) and C (----) fibre blockade of specific concentrations of three agents dissolved in either HEPES-Liley (○) or carbonated-Liley (●) solution. Desheathed rabbit vagus *in vitro*, 23–26 °C, pH 7.4.

adjacent Schwann cells do not overlap, a number of processes from those adjacent Schwann cells were found to interdigitate across the node (Peters and Vaughn, 1970). The lower sensitivity of A fibres to osmotic effects (Dodt, Forke and Zimmerman, 1983) is further evidence of the presence of barriers to diffusion.

A drug of high lipid solibility will pass easily through these lipoprotein diffusion barriers and rapidly block A fibres compared with C fibres. Low lipid solubility drugs will block C fibres without difficulty, since they have relatively few diffusion barriers around them, but will take considerably longer to reach the A fibre axon. Eventually the greater susceptibility of the latter will become apparent. This study has demonstrated this relative effect across a range of drugs with different lipid solubilities, the carbonated solution serving mainly to speed diffusion. During drug washout, the process was reversed. Even with procainamide, the time course of recovery of C fibres was measured in minutes, but for A fibres it took hours.

Another physico-chemical factor besides lipid solubility may be relevant. The pKa of amethocaine is 8.48, that of procainamide 9.26. At physiological pH, approximately 6% of amethocaine will be present as the un-ionized lipid soluble form, whereas for procainamide the figure is 1%. This difference may well contribute to the greater rate of penetration of amethocaine through lipid barriers. The pKa of the other drugs lie between these extremes (table II), although that for di-MAPA is close to that for amethocaine in spite of the fact that it is the second least potent agent in the series. In addition, amethocaine is many times more potent than procainamide than the ratio of their un-ionized concentrations would predict.

The above analysis explains the effects of these agents on this *in vitro* nerve preparation. At first sight, it does not seem to resolve the contradiction between laboratory and clinical work referred to earlier. The earliest laboratory work on differential nerve sensitivity to local anaesthetic was performed in the 1920s (Gasser and Erlanger, 1929) and is usually quoted as having shown that C fibres were more sensitive to cocaine than A fibres. What was actually stated was that "small fibres are blocked *before* [our italics] larger ones". Gasser and Erlanger went on to infer that this was the result of nerve susceptibility, but raised the possibility that differences in myelin sheath thickness may have been relevant. Since they were using concentrations of cocaine that completely blocked nerve conduction, they were observing the relative rate of blocking of different fibre types, rather than absolute sensitivity. Similarly, Heinbecker, Bishop and O'Leary (1934) used concentrations of procaine, both *in vitro* and clinically, that produced complete blockade.

Clinical situations arise in which evidence of blockade of some functions served by A fibres (light touch and motor power) does not develop with low concentrations of local anaesthetics. This is the basis of the technique of differential intrathecal blockade with procaine, used in the diagnosis of chronic pain states (Miller, Munger and Powell, 1980). Procaine is of relatively low lipid solubility and, in the absence, of potentiation by a carbonated preparation, blocks C fibres more quickly *in vitro* than A fibres (fig. 8). *In vivo* application would similarly block C fibres fairly quickly, but in the intact preparation the capillary circulation through the nerve might remove drug at a rate faster than it could pass through the diffusion barriers around A fibres. Application of a high concentration would enable the drug to penetrate these barriers at a faster rate than the circulation removes it, so that complete blockade results. Just to maintain minimal blockade, Sarnoff and Arrowood (1946), the pioneers of differential spinal block, had to use intrathecal infusions of dilute procaine, presumably because of removal of drug by the circulation.

In the extradural space the barriers to drug diffusion are even greater, since the nerve is surrounded by a sheath that is derived from the dura mater. Even a much more lipid soluble drug might penetrate that barrier only at a rate sufficient to block C fibres (Gissen, Covino and Gregus, 1982). Adjustment of dose and frequency of administration of bupivacaine in obstetric extradural practice demonstrates that effect regularly. In clinical practice only the most lipid soluble agents can penetrate nerves fast enough to demonstrate true axon sensitivity.

The most lipid soluble agent to reach clinical use to date is etidocaine, and from an early stage it was noted that: "Motor blockade was strongly intense compared to the marginally effective sensory analgesia" (Bromage, Datta and Dunford, 1974). This fits the theory that a highly lipid soluble agent can penetrate rapidly the diffusion barriers around A fibres (thought to control voluntary muscle) and that their greater sensitivity will result in a more marked effect than on C fibres (carrying pain sensation). Recent *in vivo* animal work has confirmed that etidocaine can block A fibres faster than C fibres (Ford et al., 1983).

This study has examined the *in vitro* sensitivity to amino-ester local anaesthetics of the nerve fibre types in rabbit vagus nerve and has confirmed the finding of previous work with amide drugs (Gissen, Covino and Gregus, 1980) that A fibres are the most sensitive and C fibres the least. The drugs studied varied considerably in potency, and in the rate at which A fibre blockade developed. Both effects may be related to lipid solubility—the higher the solubility, the higher the potency and the faster blockade developed.

Relating these results to previous *in vivo* animal and clinical studies has indicated that the traditional views on the susceptibility of different nerve fibre types may have resulted from confusion of absolute axon sensitivity with rate of penetration of diffusion barriers. It is an interesting speculation worthy of further investigation that, when blockade of only modalities of sensation carried by C fibres is required, a drug of low lipid solubility might have advantages. Procainamide is often thought to have no local anaesthetic activity, and its action has been studied rarely. Newman and Clark (1950) found that it did not produce sciatic nerve blockade (where diffusion barriers are great) in the dog, but that it could last twice as long as procaine when used by infiltration.

ACKNOWLEDGEMENTS

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NITROUS OXIDE AND WOUND HEALING*

T. A. ALGIE, A. SETH, J. C. BARBENEL, D. J. GALLOWAY, W. M. GRAY AND A. A. SPENCE

SUMMARY

Following a paravertebral surgical incision, mature, female rats under ether anaesthesia were exposed to either 3% nitrous oxide, continuously for 48 h, or 50% nitrous oxide, 4 h each day for 7 days. For each exposure group, a similar number of rats was exposed to atmospheres containing no nitrous oxide. Wound healing was assessed by measurement of the breaking strengths of wound samples. No statistically significant influence on breaking strength could be attributed to nitrous oxide following either exposure sequence.

Exposure to nitrous oxide can lead to impaired production of DNA (Amess et al., 1978), an effect likely to cause disturbance in tissues undergoing rapid cell division, such as in a healing wound. We have investigated the effect of nitrous oxide exposure on wound healing in the rat, by measuring the force (breaking strength) required to produce rupture of a wound sample under standardized conditions.

MATERIALS AND METHODS

Experiment one. Twenty-four mature, female, Albino–Swiss rats were anaesthetized with ether in air and a 4-cm skin incision was made in a paravertebral area which had been confirmed as an area of active hair growth. The wounds were closed using interrupted silk sutures at 5-mm intervals.

Twelve rats were placed in a specially adapted plastic container, with a Perspex lid and an internal volume of 90 litre. The fresh gas flow into the container was nitrous oxide 66 ml min^{-1} and air 2.2 litre min^{-1}. This gave a nominal concentration of 3% nitrous oxide. The remaining 12 rats (controls) were placed in a similar container and exposed to air 2.25 litre min^{-1} only. All the animals were allowed free access to food (Oxoid Breeding Diet) and water throughout the period of exposure.

Concentrations of nitrous oxide, carbon dioxide and oxygen were measured at regular intervals, both within the container and at the exhaust port, using a Bedfont TM40 nitrous oxide analyser, a Hartmann and Braun URAS4 carbon dioxide analyser and a Servomex OA570 oxygen analyser. After 48 h the animals were removed from the containers and returned to their normal animal house environment.

Between the 15th and the 18th day following incision, the animals were killed using an overdose of ether, and an area of skin containing the healing wound was removed and stored in Ringer's lactate solution.

Experiment two. Forty rats were prepared as before. Twenty were exposed to 50% nitrous oxide in oxygen, using a fresh gas flow of Entonox 9 litre min^{-1}, for 4 h each day for 7 days. A control group (20 rats) was exposed to 50% nitrogen in oxygen, using a fresh gas flow of air 5.75 litre min^{-1} with oxygen 3.25 litre min^{-1}, for similar periods. On the 8th day the animals were killed and skin specimens prepared as before.

Wound breaking strength was determined using a modification of the method of Than Than and others (1979) using an Instron tensile test machine (TT-CM, Instron Limited, High Wycombe, Bucks). Three samples from each wound were tested, as fol-

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lows. Using a multi-bladed template the skin was cut into parallel strips, each 3 mm wide. All visible sutures were carefully removed and the test strip mounted in spring-loaded grips. The length of specimen between the grips was 25 mm, with the wound in the middle of the strip. The specimen, immersed in Ringer's lactate solution, was stretched at a constant rate of 50 mm min^{-1} until rupture occurred. The force applied to the skin sample was measured continuously and the force applied at the time of rupture taken as the breaking strength. The results obtained were analysed using the Wilcoxon–Mann–Whitney U test, using the two-sided P value.

RESULTS

In experiment 1, gas concentrations in the exposure chambers were all within intended limits. Nitrous oxide varied from 2.8% to 3.25%, carbon dioxide was 2.1% and oxygen was 18.6%. In experiment 2, carbon dioxide concentrations did not exceed 0.5%.

The results for experiment 1 are given in table I. Median value for the group exposed to 3% nitrous oxide was 183.5 g and median value for the control group was 172.5 g. There was no statistically significant difference between the groups ($P = 0.15$).

In experiment 2 (table II), median value was 129 g for the group exposed to 50% nitrous oxide and 152.5 g for the control group ($P = 0.25$).

DISCUSSION

It is now clear that nitrous oxide is capable of oxidizing vitamin B_{12} from an active, Cob-I-alamin form, to an inactive, Cob-II-alamin form (Banks, Henderson and Pratt, 1968). This oxidation by nitrous oxide and its implications for DNA production have recently received considerable attention. As vitamin B_{12} is a co-factor for the enzyme methionine synthase, exposure to nitrous oxide can cause inactivation of this enzyme, both when given in commonly used anaesthetic concentrations to animals (Deacon et al., 1980) and to man (Koblin et al., 1982), and when given in low concentrations for long periods to animals (Sharer et al., 1983). Because of its important role in folate metabolism, decreased activity of methionine synthase can lead to impaired production of DNA, when assessed by the deoxyuridine suppression test (Amess et al., 1978; Deacon et al., 1980). As would be expected from this effect on DNA, the tissues which have so far been identified as being most at risk are those tissues in which there is rapid cell division, for example: the bone marrow (Amess et al., 1978), cells involved in sperm production (Kripke et al., 1976), and the cells of the developing fetus (Viera et al., 1980). The fibroblast proliferation which occurs in the early stages of wound healing might also be at risk from nitrous oxide toxicity.

TABLE I. *Results of experiment 1, exposure to 3% nitrous oxide continuously for 48 h. Breaking strength of wound samples (g) Three samples were tested from each wound*

	3% Nitrous oxide			Controls		
Animal No.	I	II	III	I	II	III
1	266	195	284	258	168	193
2	248	247	289	116	96	173
3	178	132	147	250	218	203
4	280	270	150	133	173	173
5	117	150	138	132	172	133
6	142	128	163	158	243	190
7	218	190	278	150	181	167
8	225	220	224	125	113	116
9	320	198	278	180	138	165
10	168	176	175	168	182	264
11	147	140	116	132	365	237
12	258	273	212	163	240	216

TABLE II. *Results of experiment 2, exposure to 50% nitrous oxide 4 h each day for 7 days. Breaking strength of wound samples (g) Three samples were tested from each wound. In the control group, breaking strengths of three samples could not be determined because of the presence of undetected sutures*

	50% Nitrous oxide			Controls		
Animal No.	I	II	III	I	II	III
1	119	260	146	153	140	143
2	122	200	129	150	152	95
3	102	124	73	136	78	110
4	70	94	89	68	—	159
5	108	133	101	160	79	120
6	245	230	100	410	265	348
7	225	225	215	—	275	410
8	115	110	136	170	255	165
9	180	215	235	192	97	123
10	190	272	160	128	182	222
11	180	110	102	112	107	—
12	129	202	187	89	182	160
13	99	106	130	60	78	165
14	99	123	120	200	160	245
15	161	59	121	85	129	138
16	158	76	146	345	380	165
17	111	127	124	157	44	200
18	164	197	124	80	124	102
19	183	159	176	186	186	120
20	64	63	143	27	136	345

The measurement of breaking strength has been used previously as an index of wound healing. Breaking strength of skin wounds was decreased, in animals, by cancer chemotherapy (Devereux et al., 1979), by pressure ischaemia (Lauritzen, Bagge and Bjursten, 1981) and following laparotomy (Thàn

Than et al., 1979). However, a standardized technique is important if consistent results are to be obtained (White et al., 1971).

Parbrook (1967) measured breaking strength after prolonged exposure to nitrous oxide. The tensiometric techniques available at that time were crude in comparison with the method used in this study, and so may have been unable to detect a small change in the quality of wound healing. Shah and others (1978) made a histological examination of wounds from rats exposed to nitrous oxide and found no difference from controls, but this type of assessment would be unlikely to detect minor alterations in wound healing.

In the present study, nitrous oxide produced no detectable change in wound healing, compared with controls, in either experiment. Breaking strength of the wounds showed considerable variability. The ratios of the standard deviation to the mean of the results for both the exposed and the control groups were, however, comparable to those obtained in similar tests by Glaser and others (1965), Parbrook (1967) and Than Than and colleagues (1979).

By testing wound samples during the 3rd week (experiment 1) and at the start of the 2nd week (experiment 2) following the skin incision, we hoped to detect any change in the rapid increase in wound strength which occurs during the first 2 weeks of wound healing (Sandberg and Zederfeldt, 1963). In experiment 1, testing of wound samples was spread over 4 days. This prevented the interval between obtaining samples and tensile testing from becoming excessively long. In experiment 2, exposure to nitrous oxide was staggered in such a way as to allow all animals to be killed on day 8 of the experiment.

By using a low concentration of nitrous oxide in experiment 1, it was hoped to avoid the high mortality which has been found by some workers when rats are exposed to high concentrations of nitrous oxide for prolonged periods (Green and Eastwood, 1963), but still produce significant inactivation of methionine synthase (Sharer et al., 1983). However, because this exposure produced no detectable effect on breaking strength, and because we were unable to measure methionine synthase activity directly, it was decided to use (in experiment 2) a considerably higher concentration of nitrous oxide and to extend the exposures over a much longer period.

In both experiments, standardized techniques for wound production, preparation of the final specimens and the use of an accurate and repeatable method of tensile testing, were intended to ensure the best opportunity of detecting any change in the quality of wound healing that occurred. The fact that we could find no effect of nitrous oxide exposure, even when, as in experiment 2, the exposure to nitrous oxide would be sufficient to reduce methionine synthase activity dramatically for the entire period of the study, would suggest that nitrous oxide is unlikely to have an important clinical effect on wound healing.

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NITROUS OXIDE INHALATION DOES NOT INFLUENCE PLASMA CONCENTRATIONS OF β-ENDORPHIN OR MET-ENKEPHALIN-LIKE IMMUNOREACTIVITY

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SUMMARY

The possibility that nitrous oxide releases endogenous opioid peptides into the circulation has been tested in 10 pain-free, unstressed volunteers breathing 30% nitrous oxide in oxygen. Despite achieving plateau concentrations in venous blood, accompanied by subjective effects, there were no significant changes in plasma concentrations of immunoreactive β-endorphin, methionine-enkephalin or ACTH. These results indicate that, in the absence of nociceptive input, the effects of the inhalation of nitrous oxide are unrelated to alterations in peripheral concentrations of these endogenous opioid peptides.

Although the actual mechanism by which nitrous oxide produces analgesia remains unknown, there have been a number of reports (Berkowitz, Finck and Ngai, 1977; Chapman and Benedetti, 1979; Gillman, Kok and Lichtigfeld, 1980; Yang, Clark and Ngai, 1980) of the antagonism of nitrous oxide analgesia by the opiate receptor antagonist, naloxone. This suggests that endogenous opioid systems may be involved in the mechanism of the analgesia produced by nitrous oxide.

Recently, it was demonstrated that women in labour who received 50% nitrous oxide in oxygen as the sole analgesic agent had higher plasma concentrations of β-endorphin-like immunoreactivity (βLI) than those receiving pethidine, lumbar extradural blockade, or a combination of these (Thomas, Fletcher and Hill, 1982). These authors suggested that the administration of nitrous oxide during labour was accompanied by the release of β-endorphin (βE) into the circulation, and that higher concentrations of plasma βE following the administration of nitrous oxide might be an indication of the mechanism of its action. However, interpretation of these results is complicated by the recognized influences of stressful stimuli on plasma βE concentrations (Guillemin et al., 1977; Dubois et al., 1982).

In order to avoid such influences, we have measured the plasma concentrations of the endogenous opioid peptides βE and methionine-enkephalin (met-enkephalin, ME) in 10 normal, pain-free volunteers before and 20 min after the inhalation of a mixture of nitrous oxide in oxygen. Immunoreactive ACTH concentrations were also measured, to quantify any contribution of stress in these subjects.

SUBJECTS AND METHODS

Ten healthy volunteers (five male) aged 24–39 yr gave informed consent to take part in the study. Subjects attended the research laboratory on the morning of the day of investigation. An 18-s.w.g. cannula was inserted to a vein on the dorsal aspect of the forearm after infiltration with 1% lignocaine, and flushed with heparin–saline solution. The subjects then left the laboratory and continued their usually daily routine. They returned at 14.00 h and were made comfortable on a couch, Thirty millilitre of blood was sampled to measure basal concentrations of immunoreactive βE, ME and ACTH. The samples were transferred into chilled 10-ml lithium–heparin tubes and centrifuged at 2000 rev min^{-1} at 4 °C. The tubes for the ME sample were primed with aprotinin 500 μl. After spinning for 10 min, the supernatant plasma was pipetted into chilled plastic tubes, flash-frozen in

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solid carbon dioxide, then stored in a deep freeze at −70 °C. The plastic tubes for ME assay were primed with glycine hydrochloride buffer 750 μl. Measurement of plasma concentrations of βE, ME and ACTH in thawed plasma samples was performed by radioimmunoassay (Jeffcoate et al., 1978; Clement-Jones et al., 1980a; Rees et al., 1971). The between assay coefficients of variation for the βE, ME and ACTH assays were, respectively, 12%, 10% and 8%, and the sensitivites of the assays were 10 pg ml^{-1}, 5 pg ml^{-1} and 10 pg ml^{-1}, respectively. The radioimmunoassay for βE shows equimolar cross reaction with β-lipotropin (β-LPH).

After the baseline samples had been obtained the subjects inhaled a mixture of 30% nitrous oxide in oxygen by mouthpiece from a Quantiflex dental anaesthesia machine. A nose clip was used to prevent dilution of the gas mixture with room air. Two-millilitre blood samples were taken at 5-min intervals into Hamilton gas-tight syringes containing heparin 1000 i.u. ml^{-1}, in the deadspace. Nitrous oxide concentrations were estimated on these samples by gas chromatography using a technique developed in our laboratory which gives a between-assay coefficient of variation of 1.3–2.2% (Saloojee and Cole, 1978).

After 20 min, when the blood concentration would be expected to have reached a plateau of >95% of the alveolar concentration (Eger et al., 1966; Hinds, Ellis and Saloojee, 1978), further blood samples were taken, and the nitrous oxide discontinued.

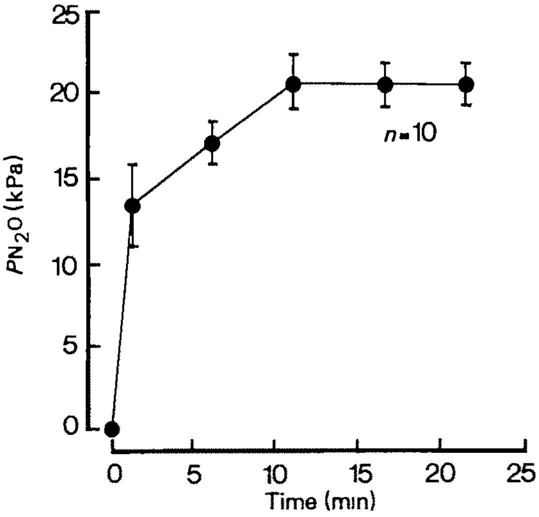

FIG. 1. Partial pressure of nitrous oxide in venous blood (kPa) (means ± SEM). Inhalation of 30% nitrous oxide in oxygen commenced at 0 min.

RESULTS

The partial pressure of nitrous oxide reached a plateau concentration of 20.9 ± 1.6 kPa (mean ± SEM) 11 min after commencing inhalation (fig. 1). All volunteers reported a subjective feeling likened to alcoholic intoxication.

In nine of the 10 subjects, basal ACTH concentrations were less than 80 pg ml^{-1} (fig. 2). In one subject, the concentration was 87 pg ml^{-1}, and this individual also had an increased concentration of βLI (290 pg ml^{-1}; this value has been omitted from figure 3). In other individuals, basal concentrations of βLI were found to range from 14 to 124 pg ml^{-1} (fig. 3).

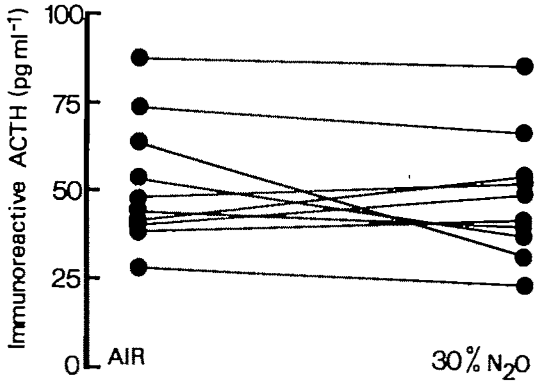

FIG. 2. Plasma concentrations of immunoreactive ACTH (pg ml^{-1}) before and after inhalation of 30% nitrous oxide in oxygen.

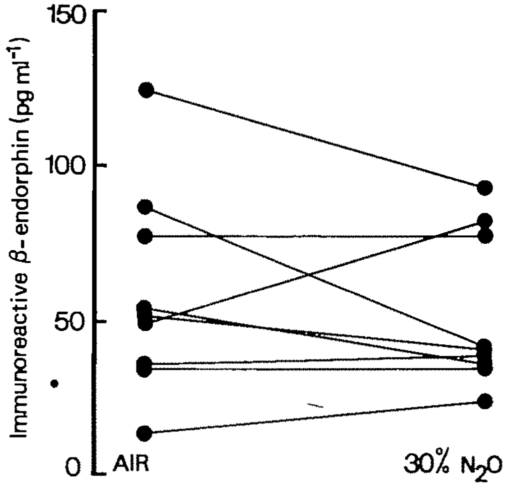

FIG 3. Plasma concentrations of immunoreactive β-endorphin (pg mg^{-1}) before and after inhalation of 30% nitrous oxide in oxygen.

Immunoreactive ME concentrations were found to range from 8 to 153 pg ml^{-1} in nine subjects (fig. 4), although in one individual a value of 237 pg ml^{-1} was obtained.

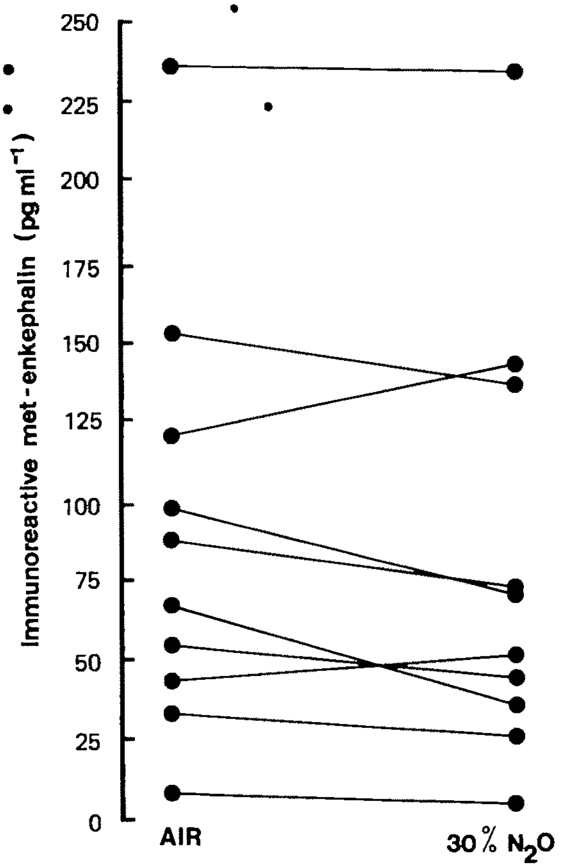

FIG. 4. Plasma concentrations of immunoreactive met-enkephalin (pg ml^{-1}) before and after inhalation of 30% nitrous oxide in oxygen.

There were no significant changes ($P > 0.05$, paired *t* test) in plasma concentrations of immunoreactive ACTH, βE or ME in response to the inhalation of nitrous oxide (figs 2, 3, 4).

DISCUSSION

β-Endorphin is derived, with ACTH, from the pituitary precursor pro-opiomelanocortin (POMC) and the peptides are secreted concomitantly in stress (Guillemin et al., 1977). Foot-shock-induced stress increases the blood concentration of βE in rats (Rossier et al., 1977) whilst in humans, increases in the plasma concentrations of βE are associated with a variety of stressful situations, including hypoxia (Yanagida and Corssen, 1981), surgery (Dubois et al., 1982) and labour (Steinbrook et al., 1982; Thomas, Fletcher and Hill, 1982; Abboud et al., 1983).

The basal concentration of βLI measured in nine of our 10 subjects ranged from 14 to 124 pg ml^{-1}. This was in keeping with the original findings of Jeffcoate and his colleagues (Jeffcoate et al., 1978), who described a range of 25–200 pg ml^{-1} in normal individuals at 09.00 h, decreasing through the day to a range of <20 – 80 pg ml^{-1} by 23.00 h. It was discovered on questioning the subject in whom the basal concentration was increased to 290 pg ml^{-1} (associated with an ACTH concentration of 87 pg ml^{-1}), that he had become involved in a rather stressful argument shortly before the basal blood samples were taken!

Immunoreactive ME circulates in human plasma (Clement-Jones et al., 1980b) and is widely distributed in the central and peripheral nervous systems (Hughes, Kosterlitz and Smith, 1977). Within the adrenal medulla, high concentrations of ME are found in association with catecholamines in chromaffin cells (Viveros et al., 1979) and, in dogs, splanchnic nerve stimulation induces secretion of ME (Hexum et al., 1980). The plasma concentrations of met-enkephalin-like immunoreactivity (MLI) are increased in canine endotoxin shock (Evans et al., 1984) and have been described in normal women during exercise (Howlett et al., 1984), in the syndrome of chlorpropamide-alcohol flush (Medback et al., 1981) and in renal failure (Smith et al., 1981).

In nine of our subjects, the basal concentrations of MLI ranged from 8 to 153 pg ml^{-1}, and accord with the original study by Clement-Jones and colleagues (1980b), who found concentrations of 14–140 pg ml^{-1} in a group of 20 normal volunteers. Our 10th subject was found to have a basal concentration of 237 pg ml^{-1}. She was in all respects normal and had not exercised before blood sampling. We can offer no explanation for her high basal MLI concentration.

Antagonism of the effects of nitrous oxide by naloxone has been demonstrated in both animals (Berkowitz, Ngai and Finck, 1976; Berkowitz, Finck and Ngai, 1977) and man (Chapman and Benedetti, 1979; Gillman, Kok and Lichtigfeld, 1980; Yang, Clark and Ngai, 1980). Whilst this could indicate activation of endogenous opioid systems, it has also been suggested (Gillman and Lichtigfeld, 1983; Gillman, 1984) that nitrous oxide may act directly as an agonist at opiate receptors. This theory is supported by evidence that prolonged exposure of rats to 80% nitrous oxide decreases opiate receptor density in the brainstem (Ngai and Finck, 1982).

If nitrous oxide were to release endogenous opioid peptides within the central nervous system, this might produce measurable changes in cerebrospinal fluid (CSF) which would not necessarily be reflected in peripheral plasma. Under normal circumstances, the blood–brain barrier is relatively impermeable to enkephalin peptides, as it is to other neurotransmitters (Cornford et al., 1978). This is borne out in obstetric patients during pregnancy and labour, in whom plasma and CSF concentrations of βLI are dissociated (Steinbrook et al., 1982). Conversely, a correlation between plasma and CSF concentrations of βE has been demonstrated by Smith and colleagues (1982), although their study was performed in patients with severe head injury in whom the blood–brain barrier may have been disrupted. Therefore, the extent to which changes in systemic concentrations of endogenous opioid peptides reflect alterations within the central nervous system is unclear. A direct measurement of endogenous opioid activity in CSF has been obtained in patients undergoing general anaesthesia which included 70% nitrous oxide (Way et al., 1982). Although the use of other anaesthetic agents may have influenced the results of this study, no measurable increase in CSF concentration of βE was found.

Whilst any changes in the concentrations of endogenous opioids in response to the administration of nitrous oxide might conceivably be influenced by nociceptive input, this study was designed to investigate the effects of the agent in the absence of such stimuli. To this end, i.v. cannulae were inserted several hours before blood sampling began, and the experiment was performed on quiet, resting volunteers. As a result, ACTH concentrations were within the normal range in nine of the subjects. The influence of diurnal variation on peptide concentrations was avoided by sampling at the same time of day in each individual.

Under these controlled conditions, we have been unable to demonstrate any peripheral reflection of the release of βE or ME as a result of the inhalation of nitrous oxide. This supports the negative findings in CSF reported by Way and colleagues (1982). However, our results cannot exclude a direct action of nitrous oxide at opiate receptors or, indeed, the nitrous oxide-mediated release of other peptides.

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IN VIVO INTERACTIONS BETWEEN THE BENZODIAZEPINE ANTAGONIST Ro 15–1788 AND THE STEROID ANAESTHETIC ALTHESIN IN RATS

B. WARDLEY-SMITH AND H. J. LITTLE

SUMMARY

Althesin and Δ16-alphaxalone have been used alone and in combination with the benzodiazepine antagonist Ro 15-1788 to investigate any protective effect these drugs might have against bicuculline-induced convulsions in rats. We found that Althesin provided good protection against bicuculline-induced convulsions which was enhanced when Ro 15-1788 was also present. Δ16-Alphaxalone lacks the anaesthetic properties of Althesin, but did have some activity in preventing bicuculline-induced convulsions, although it was less effective than Althesin. Its action was not enhanced by treatment with Ro 15-1788. Although we have no definitive explanation of these results, it is possible that when Ro 15-1788 is used clinically, it may interact with other drugs not related chemically to the benzodiazepines.

Althesin and ketamine can provide considerable protection against convulsions produced by the γ-aminobutyric acid (GABA) antagonist bicuculline and the glycine antagonist strychnine (Wardley-Smith, Little and Halsey, 1983), and against convulsions caused by high ambient pressure (Bailey et al., 1977; Green, Halsey and Wardley-Smith, 1977). There has been little investigation of the mechanism of this anticonvulsant effect, although the potent protection provided by Althesin against bicuculline-induced seizures suggests that the GABA–receptor complex (fig. 1) might be a possible site of action. The complex is thought to contain three separate types of receptor—for GABA, benzodiazepines and barbiturates—the last two drug groups causing potentiation of the effects of GABA.

The studies reported here were designed to investigate any activity of Althesin at the GABA complex by using the competitive benzodiazepine antagonist Ro 15-1788. This antagonist has been shown to prevent the pharmacological effects of the benzodiazepines (Hunkler et al., 1981), including their anticonvulsant action, but not the anticonvulsant effect of barbiturates, which do not bind to benzodiazepine receptors (Nutt, Cowen and Little, 1982). In addition, it has been shown to prevent the protective effects of flurazepam on pressure-induced convulsions (Bichard and Little, 1982). There do not appear to have been any studies of the interactions between anaesthetic steroids and benzodiazepine receptors, although a steroid compound, an androstan-11-one derivative (R 5135), has been shown to interfere with benzodiazepine binding (Hunt and Clements-Jewery, 1981).

Ro 15-1788 has been suggested to be of use in antagonizing the effects of overdoses of benzodiazepines and its effectiveness in clinical trials was demonstrated by Scollo-Lavizzari (1983). The interactions of Ro 15-1788 with non-benzodiazepine drugs have not been extensively studied, but its possible antagonism or potentiation of anaesthetics are of clinical relevance.

In the present studies we investigated the effects of Althesin alone, and in combination with Ro 15-1788, against convulsions in rats produced by the competitive GABA antagonist, bicuculline. This drug blocks the GABA receptor and, thus, the convulsions result from a reduction in inhibitory transmission. When we found that an interaction occurred between Althesin and Ro 15-1788, we carried out corresponding experiments with Δ16-alphaxalone. Alphaxalone is the principal con-

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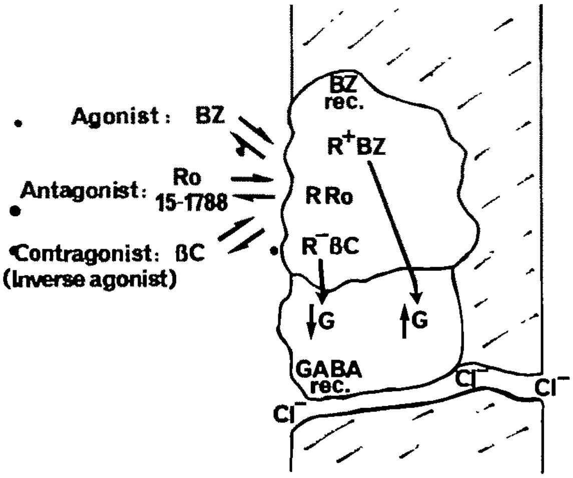

FIG. 1. Diagram of the theoretical model for the benzodiazepine–GABA–receptor–ionophore complex. Action of GABA (G) at its receptor site causes an increase in chloride (Cl$^-$) conductance. This can be modified by drugs acting at the benzodiazepine receptor: increased by benzodiazepines (BZ), decreased by benzodiazepine contragonists (inverse agonists) (βC) and unaltered by Ro 15-1788 which antagonizes the actions of the former groups of drugs. The benzodiazepine receptor, the GABA receptor and the ionophore are all thought to be components of a single protein entity.

stituent of Althesin, and Δ16-alphaxalone is a structural analogue. The change in the analogue consists only of a double bond instead of a single bond between C16 and C17, but this results in a considerable difference between the pharmacological properties of alphaxalone and Δ16-alphaxalone. The original investigations on Δ16-alphaxalone (Phillipps, 1974) failed to show any generalized anaesthetic activity, up to a dose of 200 mg kg^{-1} in mice, and as far as is known, it is not metabolized to any active compound.

MATERIALS AND METHODS

Female Sprague–Dawley rats (weight range 180–250 g) were used in all experiments. A 22-gauge Abbocath T catheter was inserted to a lateral tail vein under "light" halothane in oxygen anaesthesia and taped securely in place. A rectal probe was inserted to enable temperature to be measured and to be maintained at 37 ± 1 °C by means of a heated blanket. The rat was placed in a small restraining cage and allowed to wake up.

In all experiments, after the appropriate drug pretreatment, bicuculline was infused i.v. Bicuculline (Sigma) was dissolved in hydrochloric acid 0.1 mol litre^{-1} to give a concentration of 1 mg ml^{-1}. It was titrated back to pH 3.0 with sodium hydroxide 1 mol litre^{-1} and stored at 0 °C until required. Immediately before use, the stock solution was diluted with saline to give a final concentration of 0.1 mg ml^{-1} at pH 3.0. An infusion pump (Braun Perfusor) was used to provide a stable infusion rate of 1.6 ml min^{-1}; preliminary experiments indicated that this speed gave reproducible results, with control rats developing myoclonic twitching 30–40 s after the start of infusion. We took the first gross myoclonic twitch of the whole body as the endpoint; all rats developed myoclonus but some of the drug treatments prevented the appearance of full seizures, which made the latter unsuitable as an endpoint. Once the first myoclonic twitch had occurred, the rat was killed immediately with an overdose of anaesthetic.

Althesin

After insertion of the catheter, Althesin (alphaxalone 9 mg ml^{-1} and alphadolone acetate 3 mg ml^{-1} in 20% Cremophor El; Glaxo Ltd) was infused using a small syringe driver (Pye MS16). The mean dose of Althesin was 0.62 ±0.02 (SD) mg kg^{-1} min^{-1}; in each rat the dose was determined to be sufficient to prevent gross response to a 10-V electrical stimulus applied to the proximal 2.5 cm of the tail. After a 15-min stabilization period for Althesin, Ro 15-1788 (Roche Products Ltd) 10 mg kg^{-1} or its Tween vehicle was injected i.p. After a further 15 min, bicuculline was infused simultaneously with Althesin by means of a Y-piece, and the time to the first myoclonic twitch recorded.

Δ16-Alphaxalone

Δ16-Alphaxalone (3α-hydroxy-5αpregn-16-ene-11, 20-dione; Glaxo Ltd) proved to be almost insoluble in Cremophor. A suspension of 30 mg ml^{-1} was prepared by grinding Δ16-alphaxalone in a pestle and mortar, suspending in 20% Cremophor El in saline and sonicating for 1 min. This proved to be too viscous to be injected reliably from the syringe driver and was injected manually as described below.

On awakening from the initial anaesthetic, the rat was injected i.p. with Ro 15-1788 10 mg kg^{-1} or its Tween vehicle as a control, and then placed in a small restraining cage. Δ16-Alphaxalone 1 ml (mean dose 137 ± 19 (SD) mg kg^{-1}) or Cremophor 1 ml alone (controls) was injected manually over 10 min; as soon as this was completed, the infusion of bicuculline 1.6 ml min^{-1} was commenced, and the time to the first myoclonic twitch recorded.

In some experiments, rats receiving Δ16-alphaxalone became somnolent, with partial loss of righting reflex, although they did not become fully anaesthetized. Therefore, the purity of the isomer was verified using infra-red and ultra-violet spectrometry and thin-layer chromatography; results showed that there were no impurities in the Δ16-alphaxalone which could account for this (G. H. Phillipps, Glaxo Group Research Ltd; personal communication).

Bicuculline controls

One group of rats received no pretreatment in order to provide comparison with the group which received the vehicles for Ro 15-1788 and Δ16-alphaxalone; 15 min after insertion of the catheter, bicuculline was infused and the time to the first myoclonic twitch recorded.

Treatment groups

The following combinations of drugs were used to treat the rats before the infusion of bicuculline:

(1) Ro 15-1788 + Althesin
(2) Tween + Althesin
(3) Ro 15-1788 + Δ16-alphaxalone
(4) Tween + Δ16-alphaxalone
(5) Ro 15-1788 + Cremophor
(6) Tween + Cremophor
(7) No pretreatment

Results were analysed using the Mann-Whitney *U*-test.

RESULTS

Results are shown in figure 2. Both groups of rats which received Althesin were well protected against the bicuculline-induced seizures, such that the amount of bicuculline required (relative to the appropriate control) was increased by more than 240% ($P < 0.001$). In addition, there was significantly greater protection against seizures when Althesin was combined with Ro 15-1788 relative to Althesin + Tween vehicle, the amount of bicuculline required being increased by 24% ($P = 0.013$).

In contrast, Δ16-alphaxalone was much less effective against the bicuculline-induced convulsions, although it did have a small protective effect. The group of rats which were given Δ16-alphaxalone + Tween vehicle showed an increase of

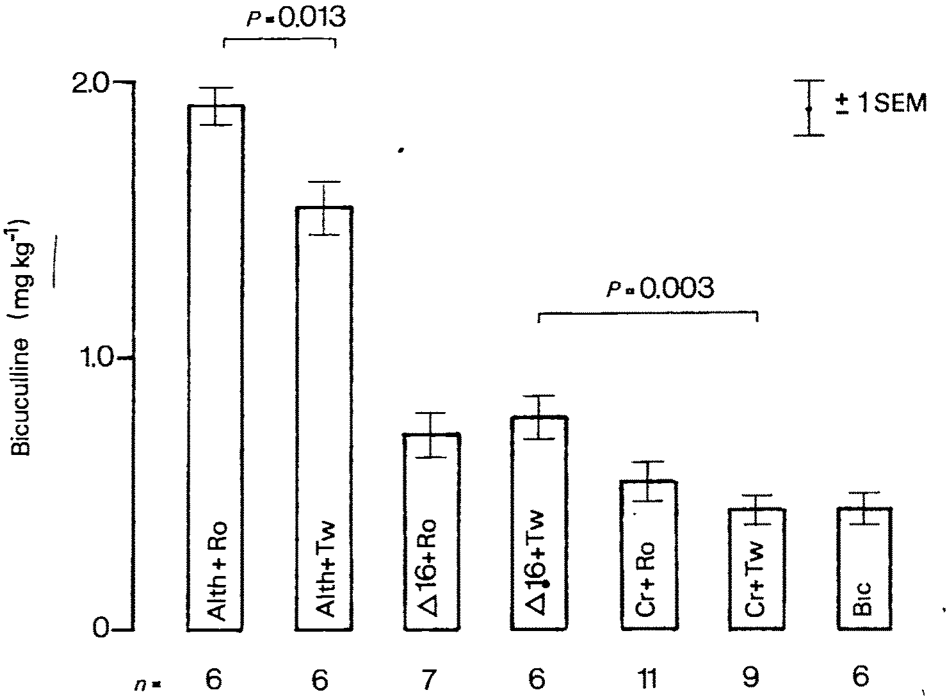

FIG. 2. Histogram showing relative effectiveness of the different combinations of drugs in protecting against bicuculline-induced seizures. *P* values obtained using Mann–Whitney *U* test. *n* = number of rats used to determine each mean value.

77% in the amount of bicuculline required relative to the control ($P = 0.003$); the group which received Δ16-alphaxalone + Ro 15-1788 showed a similar trend, which was not significant.

In contrast to the results for Althesin, there was no significant difference between the Δ16-alphaxalone groups when combined with either Tween vehicle or Ro 15-1788.

In these experiments we had three separate control groups (Cremophor + Ro 15-1788; Cremophor + Tween; no pretreatment). There were no significant differences between these groups in the amount of bicuculline required to produce seizures.

DISCUSSION

The main conclusion from this study was that Ro 15-1788, far from antagonizing the anticonvulsant effect of Althesin against bicuculline-induced seizures, actually increased this effect. No such interaction was seen when Ro 15-1788 and Δ16-alphaxalone were combined. The anticonvulsant activity of Δ16-alphaxalone seen previously in studies against the hyperexcitability caused by high pressure (Halsey and Wardley-Smith, 1983) was confirmed in the present experiments with bicuculline, and sedative actions of Δ16-alphaxalone, not reported previously, were also seen. Bicuculline is thought to cause seizures by acting as a competitive antagonist at the GABA receptor, decreasing inhibitory transmission. The basis of the high pressure excitability is not known, but the effects of anticonvulsants resemble their effects on bicuculline convulsions (Bichard and Little, 1982).

There are several possible explanations for the interaction which we found between Ro 15-1788 and Althesin. The effect may have been caused by the Cremophor solvent; a partial agonist action of Ro 15-1788 at the benzodiazepine receptor; a potentiation of the anticonvulsant effects of Althesin by Ro 15-1788 or an effect of the antagonist on the metabolism of Althesin.

The interaction between Ro 15-1788 and Althesin did not appear to be related to the Cremophor solvent because the solvent vehicle alone did not increase the convulsion thresholds to bicuculline either when given alone, or when combined with Ro 15-1788. The benzodiazepine antagonist has been shown to have "partial agonist" anticonvulsant effects when given alone at very high doses (50 mg kg^{-1}), but no anticonvulsant effect of the 10-mg kg^{-1} dose was seen when given alone (Nutt, Cowen and Little, 1982), or when combined with Cremophor in the present studies. It is conceivable that this partial benzodiazepine agonist action of Ro 15-1788 is increased by the administration of Althesin, but at the present time it is not possible to say whether the interaction was the result of this or of an increase in the effects of Althesin attributable to the action of Ro 15-1788.

The lack of effect of Ro 15-1788 on the anticonvulsant effect of Δ16-alphaxalone (see below) confirms that the effect seen was the result of an interaction between Althesin and Ro 15-1788.

It is possible that this interaction may be taking place at the GABA–receptor–ionophore complex which contains the benzodiazepine receptors, but in the absence of information concerning the effects of the steroid anaesthetic on this complex this remains speculation. Scholfield (1980) has shown that alphaxalone potentiated inhibitory transmission *in vitro*, and Ro 15-1788 has been shown to potentiate the electrophysiological effects of GABA, also *in vitro* (Little, 1984). The effect of Ro 15-1788 on the anticonvulsant action of Althesin is specific to this steroid anaesthetic as no change, in either direction, was found with Ro 15-1788 when the effects of other drugs on chemically-induced seizures were examined; for example phenobarbitone (Nutt, Cowen and Little, 1982) and the GABA agonist progabide (Lloyd et al., 1981) have been studied. However, Green, Nutt and Cowen (1982) showed a non-significant increase in the anticonvulsant action of melatonin when it was combined with Ro 15-1788.

Another possible basis for the interaction is an effect on the metabolism of Althesin. The rapid metabolism of Althesin is responsible for the termination of its activity *in vivo*, but at present there is no information available concerning the effects of Ro 15-1788 on steroid metabolism in rats or man.

Δ16-Alphaxalone was not as effective as Althesin in protecting against bicuculline-induced convulsions, in spite of the fact that it was given in considerably higher concentrations than Althesin. This may have been the result of a lower intrinsic pharmacological activity, but it is also possible that less effect was seen because of its low solubility. Only a negligible amount dissolved in Cremophor, and so a sonicated suspension was used. However, Δ16-alphaxalone did increase significantly the amount of bicuculline required to cause convulsions and, thus, at least some of the drug was reaching the site of action. Δ16-Alphaxalone was shown to produce a small depression of population excitatory postsynaptic potentials in isolated guineapig olfactory cortex, but this was much less pronounced than that seen with alphaxalone (Richards and Hesketh, 1975).

The sedative properties of Δ16-alphaxalone seen in this study have not been reported previously and were not the result of impurity of the compound. Δ16-Alphaxalone was one of the compounds produced during the development of Althesin, and there has been little investigation of its properties. The rate of metabolism is not known, but in view of the fairly rapid metabolism of alphaxalone in rats (a half-life of 7 min (Child et al., 1972)) it is probable that its duration of action is relatively short. However, the bicuculline infusion was started immediately on completion of injection of Δ16-alphaxalone, and thus even if metabolism was rapid, this should not influence the results.

Ro 15-1788 has been suggested for clinical use in benzodiazepine overdose and is currently under trial for use in comatose patients who have received benzodiazepines for status epilepticus (Scollo-Lavizzari, 1983). Many of these patients will have taken or been given drugs other than benzodiazepines, and it is possible that interactions such as the one we describe here may complicate the effects of the antagonist.

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ANAESTHESIA FOR SURGERY IN A PATIENT WITH A TRANSPLANTED HEART

S. R. W. BRICKER AND J. C. SUGDEN

SUMMARY

Five-year survival following cardiac transplantation approaches 50% and such patients occasionally present for non-cardiac surgery. The application of a simple general anaesthetic technique is described in a patient undergoing minor surgery, and the problems involved in managing heart transplant recipients are discussed.

Since Barnard carried out the first human allograft cardiac transplant in December 1967, more than 450 such operations have been performed worldwide. The 5-year survival is in the region of 45–50%, and in 1981 more than 130 recipients were still alive (Rottembourg et al., 1981; Oyer et al., 1981). A small number of survivors have presented for emergency or elective non-cardiac surgery. We present our experience with a patient who received general anaesthesia for a minor general surgical procedure two-and-a-half years after undergoing heart transplant surgery.

CASE HISTORY

The patient was a male aged 36 yr who had received a heart transplant 30 months previously because of end-stage ischaemic heart disease. In general, his progress following surgery had been good; his rehabilitation was such that he had become a regular participant in charity runs. However, review coronary arteriography performed 2 years following the transplantation had demonstrated coronary artery disease, and in succeeding months the patient began to experience episodes of dyspnoea and malaise. An acute episode of breathlessness led finally to his admission for observation in October 1983. His symptoms settled rapidly and neither ECG nor the serial measurements of the concentrations of cardiac enzymes provided confirmation of myocardial infarction. Examination revealed that a fungal infection of the toe nails and groin, which had been noted some months previously, had become much more severe in spite of topical and oral anti-fungal treatment. In view of the high risk of systemic, and particularly pulmonary, involvement, it was felt that the best hope of controlling the infection was by complete avulsion of all the toe nails, and the decision was taken to proceed to surgery under general anaesthesia. Techniques which involved extradural or intradural analgesia were not considered, because of the associated hypotension and the risks of introducing infection to the central nervous system. Alternative techniques such as multiple digital nerve blockade or bilateral ankle blocks were also rejected, principally because they were unacceptable to the patient.

Before surgery, the patient's drug regimen comprised prednisolone 12.5 mg daily, azathioprine 150 mg daily, dipyridamole 100 mg 6-hourly, soluble aspirin 150 mg daily and Moduretic (amiloride hydrochloride 5 mg + hydrochlorothiazide 50 mg) one tablet daily. He weighed 67 kg and was markedly Cushingoid in appearance, despite the moderate dose of glucocorticoid. His heart rate was 90 beat min^{-1} and his arterial pressure was 140/90 mm Hg. A permanent demand pacemaker had been inserted at the time of his original transplant surgery; at his most recent attendance at the original cardiothoracic unit its function had been described as satisfactory. ECG demonstrated sinus rhythm and features suggestive of anterolateral ischaemia. His most recent coronary angiography had been per-

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formed 5 months previously and had shown the progression of early changes of coronary artery disease with irregularities in the left anterior descending, circumflex and right coronary ateries. Clinically, the patient's respiratory system was normal, and his chest x-ray unremarkable. His haemoglobin concentration was 16.2 g dl^{-1}, haematocrit 48%, white cell count 4.3×10^9 $litre^{-1}$ and platelet count 278×10^9 $litre^{-1}$. Serum electrolyte concentrations were within normal limits, with the exception of a potassium concentration (3.3 mmol $litre^{-1}$). This had been a persistent feature since transplantation, had not been correctable by oral potassium supplements and did not appear to be clinically significant. There was no obvious impairment of renal function, and liver function tests were normal.

The patient received papaveretum 10 mg and hyoscine 0.2 mg with hydrocortisone 200 mg i.m. as premedication. Anaesthesia was induced by the slow injection of thiopentone 225 mg i.v. and was maintained with 67% nitrous oxide in oxygen and halothane up to 3.5%. He was allowed to breathe spontaneously through a Magill breathing system. His Cushingoid facies exaggerated the difficulties of maintaining an airway already posed by his naturally stout build, and a Guedel oropharyngeal airway was required to prevent respiratory obstruction. Monitoring of vital signs was achieved using an oscillotonometer for arterial pressure measurement, a pulsemeter, an electrocardiograph and a precordial stethoscope.

His systolic arterial pressure decreased from 120 mm Hg immediately before induction to 100 mm Hg, and stabilized at 110 mm Hg for the remainder of the surgical procedure, which lasted for 23 min. The heart rate increased from its preoperative value of 92 beat min^{-1} to a maximum of 112 beat min^{-1}. Before the operation the ECG showed numerous ventricular ectopic beats which were confined to two foci and were not accompanied by any further decrease in systolic arterial pressure. Anti-arrhythmic drugs were immediately available, but none was used. Otherwise the anaesthetic course was uneventful. No significant blood loss resulted from surgery.

The patient awakened in the recovery room and was transferred back to a general medical ward where his initial postoperative course was satisfactory. However, on the 3rd day after operation, he became pyrexial and complained of lethargy and malaise. There was no obvious source of infection. The symptoms resembled those which had precipitated his original admission, and because of the possibility that they represented an acute episode of rejection of his transplanted heart, he was transferred for fuller evaluation to his original cardiothoracic centre. Endomyocardial biopsy showed a mild inflammatory infiltrate which had been a persistent feature since transplantation: the concentrations of the cardiac enzymes were marginally increased, and serial ECG continued to demonstrate widespread ischaemic changes, suggesting that he might have sustained some new myocardial damage. Multiple gated scans performed at rest and during exercise revealed that left ventricular function was not grossly impaired. His symptoms resolved. At present his condition remains stable, if somewhat precarious, and he has been able to resume gentle exercise. It is possible that the general anaesthetic to which he was submitted played a part in his transient postoperative deterioration, but it seems more likely that this was part of the natural history of his transplanted heart.

DISCUSSION

The patient with a transplanted heart presents the anaesthetist with an unusual combination of problems which relate principally to alterations in cardiac pharmacodynamics and haemodynamics resulting from denervation. Of additional importance are the typically complex drug regimens of such patients and the considerable risk of infection following long-term immunosuppressive therapy.

With regard to drug treatment, this patient was typical in that he was taking corticosteroids, a primary immunosuppressive agent, anti-platelet drugs and a diuretic. The adverse effects of these drugs are well known, although the potential problems which they may present to the anaesthetist can be overstated; many patients with less dramatic conditions present with equally extensive regimens.

Immunosuppressive drugs are continued indefinitely in heart transplant patients and infection remains a major cause of mortality, accounting in a recent series for at least 32% of deaths (Bieber et al., 1981). Thus, invasive monitoring techniques, and all forms of instrumentation, should be kept to the minimum consistent with safe anaesthesia. This includes endotracheal intubation, a procedure which we did not feel was justified in this patient because of the minor nature of the surgery, and because his facies were those which typically can present problems with intubation.

Attention to asceptic technique should be paramount, and it has been recommended that all intravascular and airway equipment should be handled with sterile gloves, the patient being exposed meanwhile to the minimum number of attendants (Samuels and Kanter, 1977).

The cardiovascular status of the patient and the response to anaesthetic and surgical stress are of most immediate concern to the anaesthetist. Functional rehabilitation in many heart transplant patients appears to be good; in one series (Oyer et al., 1981) 85% of patients were considered rehabilitated in terms of their ability to return to work or to take up other comparably demanding activities of their choice. Many of them follow regular exercise programmes; as recently as 2 months before admission, the patient described above had participated in a 5-mile charity run. Nonetheless, the transplanted heart utilizes atypical adaptive mechanisms in the face of stress, and in addition, as in this patient, may be compromised by coronary artery disease. It is denervated—to date there has been no documented evidence in the human of reinnervation (Schroeder et al., 1974; Schroeder, 1979)—and is, therefore, unable to respond to neurally mediated stimuli. Nor can it give rise to ischaemic pain. However, cardiac adrenergic receptors are intact and do respond normally to circulating catecholamines (Cannom, Graham and Harrison, 1973).

At rest, the heart rate reflects the intrinsic rate of depolarization at the donor sino-atrial node and in the absence of any vagal tone is faster than normal at about 90–100 beat min^{-1} (Schroeder, 1979). Otherwise, the haemodynamic characteristics are essentially normal. Yet, when it is subjected to the stress imposed by exercise (no study of anaesthetic or surgical stress in such patients has been published), the response of the transplanted heart is different to that of the normal innervated heart. In the latter, an increase in cardiac output is mediated via neural stimuli which lead to a simultaneous increase in heart rate and contractile force of the myocardium. The denervated heart demonstrates sequential changes: there is an initial increase in left ventricular end-diastolic volume (LVEDV), which mediates an increase in stroke volume and ejection fraction by means of the Frank–Starling mechanism. The increase in left ventricular end-diastolic volume and pressure is not sustained, but the increased cardiac output is maintained by a heart rate which slowly increases over 5–6 min in response to increasing concentrations of circulating catecholamines (Schroeder, 1979).

If major surgery is contemplated, then these factors assume great importance and it is imperative that hypovolaemia be avoided and that there is ready access to methods of controlling heart rate and myocardial contractile force. The transplanted heart responds to adrenergic receptor agonists and antagonists in the same way as the normal heart, although the administration of atropine (Leachman et al., 1971) or digoxin (Goodman et al., 1975) has no effect on heart rate. In the case under discussion, significant loss of circulating volume was not a problem; the main concerns were to minimize cardiac work in a heart with accelerated graft arteriosclerosis and to avoid undue myocardial depression and the development or arrhythmia.

In the context of the last of these, a number of workers have reported an increased frequency both of atrial and ventricular arrhythmias as well as other electrophysiological abnormalities in asymptomatic heart transplant patients (Berke et al., 1973; Schroeder et al., 1974; Bexton et al., 1983). While their aetiology remains a subject of investigation, Schroeder and colleagues (1974) have demonstrated that they may be treated successfully using conventional anti-arrhythmic drugs or DC cardioversion. However, the negative inotropic effects of anti-arrhythmic agents are enhanced in the transplanted heart. The ventricular arrhythmias which were observed in our patient were judged not to be dangerous and were untreated.

With regard to myocardial depression, it can be argued that thiopentone and halothane are not the anaesthetic agents of choice. Nonetheless, there are precedents for their use under these circumstances (Kanter and Samuels, 1977) and, in addition, we considered that a familiar technique would be easier to control and be safer to use than, for example, a less frequently adopted total i.v. method of anaesthesia. There remained the possibility, moreover, that the drugs which were given would improve the balance of myocardial work and myocardial blood flow. Cardiac work is determined mainly by four haemodynamic variables: systolic arterial pressure, heart rate, myocardial contractility and left ventricular filling pressure. Coronary blood flow is dependent upon the mean perfusion pressure and the vascular resistance, a factor which includes the compressive resistance which may arrest left coronary blood flow during ventricular systole and which makes the duration of diastole so important for myocardial perfusion. The net effects of thiopentone and halothane on these complex circulatory variables are hard to predict, but in theory, and provided that the drugs cause only minimal left ventricular dilatation, the use of halothane, in particular, might decrease myocardial oxygen demand and cardiac work. However, the experimental work which might support this thesis has been conducted in the canine model (Bland and Lowenstein, 1976) and some might assert that the concentrations attained by using halothane as the main anaesthetic agent would lead to ventricular dilatation and dyskinetic contraction which would offset any improvement in myocardial energetics.

In view of the small numbers involved, presentation of cardiac transplant patients for general anaesthesia is likely to remain uncommon. At present the literature is limited to a review of 29 cases and to two case reports (Eisenkraft, Dimich and Sachdev, 1981; Kanter and Samuels, 1977), all of which have originated in the U.S.A. However, as more of these potentially challenging patients present for surgery, a body of experience should accumulate which may permit the development of techniques based upon more precise predictions of cardiovascular performance in cardiac transplant recipients undergoing general anaesthesia, possibly centring on the use of new agents with greater cardiovascular stability.

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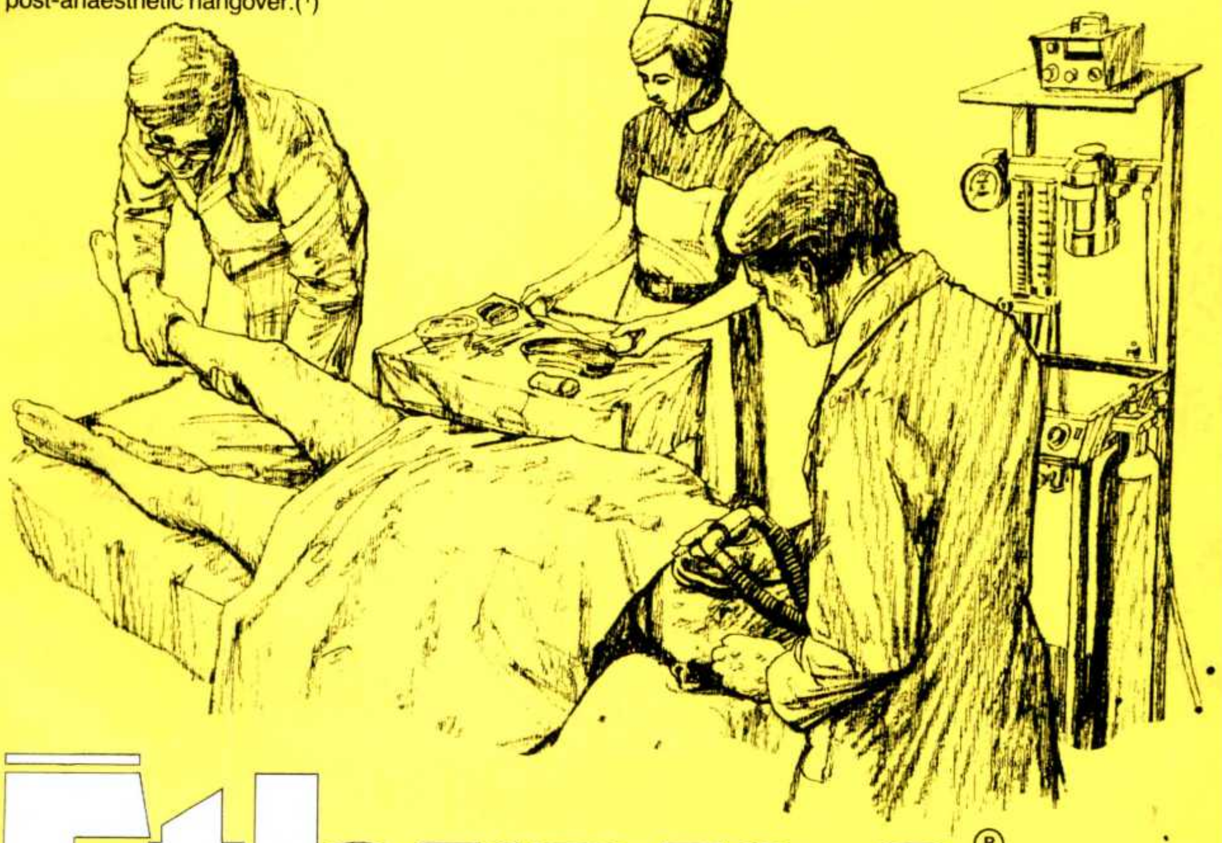

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